9-FW

Please type a plus sign (+) inside this box →

PTO/SB/21 (08-00)
Approved for use through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/768,348
Filing Date	
First Named Inventor	Rama. THEMBALATH et al.
Group Art Unit	
Examiner Name	
Total Number of Pages in This Submission	
Attorney Docket Number	Ipca Laboratories

ENCLOSURES *(check all that apply)*

- [x] Fee Transmittal Form
  - [x] Fee Attached
- [ ] Amendment / Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Assignment Papers *(for an Application)*
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [x] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) *(please identify below)*:

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm *or* Individual name	Pharmaceutical Patent Attorneys, LLC 55 Madison Avenue, 4th floor, Morristown NJ 07960-7397 USA
Signature	
Date	See below date

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on this date: see below date

Typed or printed name	Mark POHL, Reg. No. 35,325		
Signature		Date	18 June 2004

PTO/SB/17 (10-01)
Approved for use through 10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2002

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT ($) 130.00

Complete if Known	
Application Number	10/768,348
Filing Date	
First Named Inventor	Rama. THEMBALATH et al.
Examiner Name	
Group Art Unit	
Attorney Docket No.	Ipca Laboratories

METHOD OF PAYMENT

1. ☐ The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:
   - Deposit Account Number:
   - Deposit Account Name:
   - ☐ Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17
   - ☐ Applicant claims small entity status. See 37 CFR 1.27
2. ☑ **Payment Enclosed:** ☐ Check ☑ Credit card ☐ Money Order ☐ Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	740	201	370	Utility filing fee	0.00
106	330	206	165	Design filing fee	0.00
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	0.00

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES

		Extra Claims		Fee from below	Fee Paid
Total Claims	46	-20** =	26	X 9.00	= 0.00
Independent Claims	3	- 3** =	0	X 43.00	= 0.00
Multiple Dependent				0.00	= 0.00

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim, if not paid
109	84	209	42	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	0.00
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	0.00
139	130	139	130	Non-English specification	0.00
147	2,520	147	2,520	For filing a request for *ex parte* reexamination	0.00
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	0.00
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	0.00
115	110	215	55	Extension for reply within first month	0.00
116	400	216	200	Extension for reply within second month	0.00
117	920	217	460	Extension for reply within third month	0.00
118	1,440	218	720	Extension for reply within fourth month	0.00
128	1,960	228	980	Extension for reply within fifth month	0.00
119	320	219	160	Notice of Appeal	0.00
120	320	220	160	Filing a brief in support of an appeal	0.00
121	280	221	140	Request for oral hearing	0.00
138	1,510	138	1,510	Petition to institute a public use proceeding	0.00
140	110	240	55	Petition to revive - unavoidable	0.00
141	1,280	241	640	Petition to revive - unintentional	0.00
142	1,280	242	640	Utility issue fee (or reissue)	0.00
143	460	243	230	Design issue fee	0.00
144	620	244	310	Plant issue fee	0.00
122	130	122	130	Petitions to the Commissioner	130.00
123	50	123	50	Processing fee under 37 CFR 1.17(q)	0.00
126	180	126	180	Submission of Information Disclosure Stmt	0.00
581	40	581	40	Recording each patent assignment per property (times number of properties)	0.00
146	740	246	370	Filing a submission after final rejection (37 CFR § 1.129(a))	0.00
149	740	249	370	For each additional invention to be examined (37 CFR § 1.129(b))	0.00
179	740	279	370	Request for Continued Examination (RCE)	0.00
169	900	169	900	Request for expedited examination of a design application	0.00
Other fee (specify)					0.00

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** ($) 130.00

SUBMITTED BY				Complete *(if applicable)*	
Name *(Print/Type)*	Mark POHL	Registration No. *(Attorney/Agent)*	35,325	Telephone	(973) 984-0076
Signature				Date	17 June 2004

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

IN THE UNITED STATES PATENT OFFICE

In re Application of Ramachandran THEMBALATH *et al.* ("*Stabilized Paroxetine Hydrochloride Formulation*")

Serial No. 10/768,348

PETITION UNDER
37 C.F.R. § 1.102(d)

PETITION

This is a Petition under 37 C.F.R. § 1.102(d) to accelerate the examination of the captioned application.

ISSUE PRESENTED

Whether examination of this application may be made special?

RELIEF REQUESTED

Applicant respectfully requests examination of this application be made special.

FACTUAL BACKGROUND

The application presents all claims directed to a single invention. If the Office determines that all the claims presented are not obviously directed to a single invention, then the Applicant will make an election without traverse as a prerequisite to the grant of special status.

A pre-examination search has been made. A search has been made by a foreign patent office as part of the examination of the priority foreign national patent application. In addition, Applicant has made the search described below. Applicant here submits one copy

of each of the references deemed most closely related to the subject matter encompassed by the claims.

Applicant here provides a detailed discussion of the references, which discussion points out with the particularity required by 37 C.F.R. 1.111(b), (c), how the claimed subject matter is patentable over the references. In organizing this detailed discussion, Applicant first briefly reviews the pending claims, and then discusses the various references.

The Pending Claims

The application claims a moisture barrier which is uniquely suited for use with active pharmaceutical ingredients which are sensitive to degradation or discoloration when exposed to water. The moisture barrier protects the pharmaceutically active ingredient from such degradation.

An example of a moisture-sensitive drug substance ins paroxetine hydrochloride. Paroxetine is chemically described as (-)-trans-4-((4'-flurophenyl)3-3(3'4'-Methylenedioxy phenoxy methyl)-piperidine. Paroxetine has first been claimed for its antidepressant properties in US Patent No. 3,912,743 and US Patent No. 4,007,196 (assigned to Ferrosan of Denmark). Crystalline paroxetine hydrochloride hemihydrate, process for its preparation, compositions containing the same and its preparation, and its therapeutic use as antidepressant has been claimed in US Patent No. 4,721,723 and EP Patent No. 223,403. Paroxetine has been approved by the United States Food & Drug Administration for treating depression in humans.

The immediate application claims not the active ingredient, but a moisture barrier useful with paroxetine. Independent application claim 28 claims:

> 28. (New) A process for manufacturing a substantially moisture stable pharmaceutical product, comprising:
> A) mixing ethylcellulose, polar solvent, alcohol and a surfactant to make a moisture barrier pharmaceutical excipient solution;

> B) mixing a drug substance with said moisture barrier pharmaceutical excipient solution to form substantially moisture stable drug substance;
> C) coating the substantially moisture-resistant drug substance of step B in a pharmaceutically-acceptable coating.

The dependent claims address where the surfactant comprises polysorbate 80, where the drug substance comprises paroxetine, and where various components are present in specific ratios. Independent claim 33 is drawn to an article of manufacture:

> 33. (New) A substantially moisture stable drug product comprising:
> A) A substantially moisture stable core comprising a drug substance, ethylcellulose and a surfactant; and
> B) An outer layer surrounding said core, said outer layer comprising a pharmaceutically acceptable material, said outer layer substantially free of said drug substance.

The prior art identified to-date includes (1) art identified during search and examination of the priority patent application, and (2) art independently identified by the Applicant. We discuss each group of references in turn.

The Priority Application Search Results Identify
No Art Which Bars the Claims Under U.S. Law

The priority application, India Patent Application Serial No. 977/Mum/2003, has been searched and examined. That search cites one reference as most relevant: Canadian Patent No. 2,439,460. *See* EXAMINATION REPORT (14 Jan. 2004) (India Patent Office) at page 2, paragraph 2. The PCT counterpart of that patent is WO 02/069969 (copy enclosed). The '969 application confirms synopsis of the prior art given in the immediate application, and shows how it differs from the '969 application.

WO 02/069969

Manufacturing a pharmaceutical product typically entails mixing a drug substance (often called an "active pharmaceutical ingredient" or "API," or more simply an "active ingredient") with various excipients. *See e.g.*, Bristol-Myers Squibb v. Andrx Pharmaceuticals, Inc., (case No. 03-60703-CIV-HUCK, slip op. at 12 *et seq.* (4 June 2004).

Excipients provide physical bulk to the API, physically bind the tablets together, aid the tablet in dissolving *in vivo*, et cetera. Id.

Mixing excipients with the active ingredient, however, may harm the active ingredient. The '969 application describes how the active pharmaceutical ingredient paroxetine discolors when exposed to moisture. Id. at 2, lines 1 *et seq*. How to formulate a drug product has thus proved somewhat problematic.

One approach is using "extremely dry conditions" to mix powder active ingredient with powder excipients, to make the final paroxetene drug product. Id. at lines 10 *et seq*. Mixing dry or powdery mixtures, however, entails various technical problems. Id. at lines 27 *et seq*.

The '969 application thus teaches an alternative; mixing the active ingredient with the excipients using a wet granulation process, rather than dry powder mixing, to make a wet active ingredient + excipient granulate, and then "fluidizing the resulting granulate in a flow of heated dry air to dry the granulate." Id. at 3, lines 33 *et seq*. The '969 application thus entails combining the active and the excipients with water in a wet granulation process, followed by heated air drying. This approach avoids the problems inherent in mixing dry powders, yet entails added expense in drying the wet moisture, and creates the possibility that the moisture transiently present during the wet-mix process could adversely affect the active ingredient.

In contrast, the immediate application teaches coating the active ingredient with a protective ethylcellulose coating to make water-resistant granules. The coating step involves mixing the active ingredient not with wet excipients, nor with powdered excipients, but with ethylcellulose and a surfactant, together with a combination of one or more polar solvents and one or more alcohols. This approach avoids the problems inherent in the prior-art mixing of

dry powders, and also avoid the potential hydration of the active ingredient inherent to the '969 application approach.

The '969 application was published with an International Search Report. (copy enclosed) That search identifies three patents as relevant; WO 99/48499, WO 00/78288, and WO 01/58499. Each of these three references is distinguishable from the immediate application.

WO 01/58449

Patent Application No. WO 01/58449 teaches various liquid formulations of paroxetine. The combinations claimed in the '449 application (unlike those claimed in the immediate application) require paroxetine free base and a taste-masking agent. Unlike the immediate application, the '449 application does not teach use of polar solvents, nor alcohol, nor ethylcellulose, alone nor in combination.

WO 99/48499

Patent No. WO 99/48499 teaches that paroxetine free base is advantageously formulated into pharmaceutical compositions when adsorbed on or absorbed by a solid carrier. The composition of this invention is simply obtained by combining a solution of paroxetine with a suitable adsorbent or absorbent material and evaporating the solvent, for example by spray drying.

Patent Application No. WO 99/48499 thus teaches using polar solvent, as does the immediate application. The '499 application, however, also requires using paroxetine free base (a liquid oil form of paroxetine) and carboxymethylcelluose, neither of which are required in the immediate application. Further, the immediate application requires inclusion of a surfactant, a limitation not required by the '499 application.

WO 00/78288

Patent Application No. WO 00/78288 expressly teaches away from the claimed approach, teaching that the use of polar solvents is unattractive because "It is difficult to remove residual solvents from amorphous materials, such as spray dried paroxetine hydrochloride," id. at page 2, line 4 *et seq.*, and "anhydrous solvents, particularly absolute ethanol, are expensive and therefore undesirable," id. at lines 9 *et seq.*

The Applicant has Located No
Prior Art Which Bars the Claims

In addition to the search performed by the India Patent Office, Applicant has a knowledge of the prior art and, on information and belief, has caused to be made a search of the prior art. That search identifies the following additional references.

WO 99/58113

Patent Application No. WO 99/58113 teaches the dry powder mixing of the paroxetine, formulated into tablets under conditions such that there is no detectable conversion to hemihydrate. Such conditions have been achieved by the use of anhydrous or low-moisture excipients, such as dibasic calcium phosphate anhydrous (commercially available under the trade name A_TAB™), anhydrous direct-compression lactose, monosachharide sugars (*e.g.*, mannitol), disaccharide sugars (*e.g.*, lactitol, commercially available under the trademark FINLAC DC™), powdered cellulose, pregelatinised starch, microcrystalline cellulose (commercially available under the trademark AVICEL PH112™), sodium starch glycolate, croscarmellose sodium (commercially available under the trademark Ac-Di-SolF™), colloidal silicon dioxide (commercially available under the trademark SYLOID 244™ or EXPLOTAB™), magnesium stearate and talc.

The reference teaches that the paroxetine anhydrate is dry-mixed with the anhydrous or low-moisture excipients, and then compressed using standard pharmaceutical procedures.

As an additional aid to the protection of this product from the deleterious affects of moisture, the resulting tablets are film-coated using hydrophobic coating materials such as glyceryl behenate (commercially available under the trademark COMPITROL 888™) using a hot-melt coating technique.

This reference fails to teach the use of polar solvent nor alcohol alone nor in combination.

WO 99/58116

Patent Application No. WO 99/58116 teaches paroxetine hydrochloride anhydrate mixed with dry powder excipients, and dry-filling the resulting powder into a cellulose capsule shell with an intrinsically-low-moisture content (*e.g.*, those commercially available under the trademark SHIONO QUALICAPS™). The reference also teaches that dibasic calcium phosphate anhydrous and polyglycolized glycerides can be used to form oral-swallow capsules with paroxetine anhydrate which avoid the undesired conversion of the active ingredient to the hemihydrate form during the manufacturing process.

This reference fails to teach the use of polar solvent nor alcohol alone nor in combination.

WO 02/102382

Patent Application No. WO 02/102382 describes a process for preparing paroxetine hydrochloride from paroxetine base which provides paroxetine hydrochloride substantially free of pink-colored compounds or an impurity identified by an High Pressure Liquid Chromatography RRT of about 1.5.

This reference fails to teach the use of polar solvent nor alcohol alone nor in combination.

US 5,955,475

US Patent. No. 5,955,475 teaches adsorbing or absorbing paroxetine free base (the liquid oil form of the compound) onto or into a solid carrier.

This reference fails to teach the use of polar solvent nor alcohol alone nor in combination.

WO 98/31365

Patent Application No. WO 98/31365 teaches spray drying an aqueous solution of paroxetine hydrochloride. Notably, no discussion appears in the patent application regarding the problem of color development.

This reference fails to teach the use of polar solvent nor alcohol alone nor in combination.

US 6,168,805

US Letters Patent No. 6,168,805 discloses an aqueous mixture of paroxetine, water, and a pharmaceutically-acceptable polymer. The aqueous mixture is then dried to form a composition comprising amorphous paroxetine and polymer.

This reference fails to teach the use of polar solvent nor alcohol alone nor in combination. To the contrary, the reference teaches away from the immediate invention, by teaching that it is advantageous to eliminate the use of organic solvents.

WO 01/02393

Patent No. WO 01/02393 teaches an aqueous solution of paroxetine and cyclodextrin. The reference teaches that complexes of paroxetine with cyclodextrin show a high chemical stability and an improved solubility in water, and are suitable for the preparation of liquid or solid pharmaceutical compositions.

This reference fails to teach the use of polar solvent nor alcohol alone nor in combination.

US 6,503,927

US Letters Patent No. 6,503,927 describes a stable amorphous paroxetine hydrochloride composition made by dissolving paroxetine in an aqueous medium and drying the resulting solid dispersion. The reference teaches that the preferred compositions include polyvinylpyrrolidone and citric acid.

This reference fails to teach the use of polar solvent nor alcohol alone nor in combination.

WO 99/26625

WO99/26625 provides pharmaceutical formulations of paroxetine in which paroxetine is in solution in a solid, semi-solid or liquid carrier. The solutions are used to fill capsules, or self-supporting solid solutions are shaped into solid dosage forms such as tablets or pellets.

This reference fails to teach the use of polar solvent nor alcohol alone nor in combination.

WO 95/16448

Patent application serial no. WO 95/16448 reveals that earlier commercial paroxetine hydrochloride hemihydrate tablets were made using a wet granulation process. The reference teaches that the tablets so manufactured exhibit a color change; *i.e.*, the tablets develop an undesirable pink hue.

This reference fails to teach the use of polar solvent nor alcohol alone nor in combination.

US 2002065301

Published US Patent Application Serial No. US2002065301 teaches paroxetine salt compositions made with the aid of water. By controlling the pH to 6.5 or less, these wet compositions have improved stability without significant coloration problems. The reference

teaches that the suitable paroxetine salts include paroxetine hydrochloride salts, but preferably use paroxetine sulfonate salts such as paroxetine methane sulfonate.

This reference fails to teach the use of polar solvent nor alcohol alone nor in combination. The pending claims are not limited to a pH of 6.5 or less.

US 6,113,944

US Patent No. 6,113,944 relates paroxetine which is formulated into tablets using a formulation process in which water is absent. Direct compression is taught, wherein powdered paroxetine hydrochloride hemihydrate is conventionally admixed with dry excipients to make a dry powder mixture and compressed into tablets.

This reference does not teach any wet-granulate mixture, nor teach the use of polar solvent nor alcohol alone nor in combination.

US 6,007,842

The direct compression technique is also taught where paroxetine hydrochloride hemihydrate is admixed dry granulation techniques as in US Patent No. 6,007,842 where paroxetine hydrochloride hemihydrate is conventionally admixed with dry excipients and compressed into large slugs or roller-compacted into ribbon-like strands. The compacted material is then suitably milled to produce a free-flowing dry powder, which is then compressed into tablets. The excipients taught by the patent include dicalcium phosphate dihydrate (commercially available as EMCOMPRESS™ or DITAB™), microcrystalline cellulose (commercially available under the trade name AVICEL PH 102™), sodium starch glycollate (commercially available as EXPLOTAB™), and magnesium stearate.

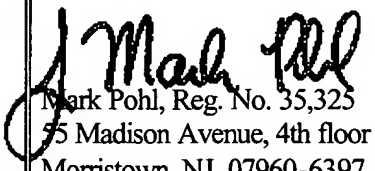
This reference does not teach any wet-granulate mixture, nor teach the use of polar solvent nor alcohol alone nor in combination.

SUMMARY

The forgoing does not provide an exhaustive enumeration of every difference between each reference and the pending claims, but does provide information adequate to show that no reference bars the pending claims.

Enclosed find (i) a photocopy of each reference discussed herein, and (ii) a FEE TRANSMITTAL FORM and the appropriate filing fee for this paper.

Respectfully submitted,
Pharmaceutical Patent Attorneys LLC



Mark Pohl, Reg. No. 35,325
55 Madison Avenue, 4th floor (P 4014)
Morristown, NJ 07960-6397 USA
17 June 2004

Direct *Mark.Pohl@LicensingLaw.Net*
☎ +1 (973) 984-0076

SD:\IPCA\paroxetine\Petition.doc

INTELLECTUAL PROPERTY INDIA
PATENTS / DESIGNS / TRADE MARKS
GEOGRAPHICAL INDICATIONS

Government of India
Ministry of Commerce and Industry

The Patent Office
Todi Estates, 3rd Floor,Sun Mill Compound
Lower Parel(West) Mumbai-400013
Tel:(091)(022)24924058,24925092,24961370
Fax No:(091)(022)24950622
Email:patmum@vsnl.net /
Web:www.ipindia.nic.in

977/MUM/2003

Date 14 JAN 2004

first examination report

To,
Gopakumar Nair Associates , ,
Nair Baugh,
Akurli Road,Kandivly (E), Mumbai – 400 101

Sub: First Examination Report
Ref. : Patent Application No: 885/MUM/2002

Name of Applicant: M/S . IPCA Labs

With reference to the request no 1996/RQ/2003 made on 24/11/2003 by you for examination, the above quoted application has been examined under section 12 of the Patents Act, 1970, as amended by the Patents (Amendment) Act, 2002 and the first statement of objection is forwarded herewith for compliance.

The documents noted in the margin are enclosed herewith for amendment in these respects and shall be resubmitted to this office within 4 months form the date of issue of this statement U/R 24(4) together with an observation that you would like to offer in connection therewith.

If any correction is made in any page of the specification that page should be freshly typed and filed in duplicate. The original pages in that case should be returned to this office duly cancelled over your signature.

The application referred to above will be deemed to have been abandoned unless all requirements imposed by the said Act and Patents Rules, 2003 are complied within 12 months U/S 21(1). No extension of time beyond 12 months is allowed.

The pages of the complete specification should be retyped wherever corrections or interpolations are made. The typed pages should preferably be on white papers in order that clear photocopies of the specification can be prepared at the time of publication of the specification.

(N. Ramchander)
Examiner of Patents & Designs
For Asst. Controller of Patents & Designs

Encl: 1) Application on form 1/1A
2) Prov. and /or complete specification
3) Prov. and /or complete drawing 4) Form 3
5) Form 5
Note : All Communication to be send to controller of Patents & Design at the above address.

PTO

1. What is claimed in Claims falls within the scope of sub clause (e) of section 3.
2. What is claimed in claims are prima facie locking in Novelty and inventive steps please refer prior publication : CA 2439460
3. Claim 3 relates to an invention distinct from the rest
4. Claim 1 does not particularly defining the invention .
5. Distinguishing features as compared with prior art given in complete specification are not clear, and the same should be pinpointed clearly.

6. A details under section 8 (1) and under in respect of corresponding foreign filing details shall be furnished.
7. A details under section 8(2) and under rule 12 (4) & (3) regarding search / examination / present status, allowed claims ,of the corresponding foreign filing should be furnished within a prescribed period or extension may be taken in form. 4 to produce the same.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 September 2002 (12.09.2002)

PCT

(10) International Publication Number
WO 02/069969 A1

(51) International Patent Classification[7]: A61K 31/445, 9/20

(21) International Application Number: PCT/DK02/00134

(22) International Filing Date: 1 March 2002 (01.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2001 00341 2 March 2001 (02.03.2001) DK

(71) Applicant *(for all designated States except US)*: **A/S GEA FARMACEUTISK FABRIK** [DK/DK]; Holger Danskes Vej 89, DK-2000 Frederiksbert (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FELUMB, Niels, Christian** [DK/DK]; Emil Slomanns Vej 3, DK-2000 Frederiksberg (DK). **HENRIKSEN, Kristian, Lund** [DK/DK]; Zolas Allé 5, DK-2860 Søborg (DK). **PEDERSEN, Søren, Bols** [DK/DK]; Vesterkærsvej 7, DK-2650 Hvidovre (DK).

(74) Agent: **RASMUSSEN, Preben**; Internationalt Patent-Bureau A/S, Høje Taastrup Boulevard 23, DK-2630 Taastrup (DK).

(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), DE (utility model), DK (utility model), DM, DZ, EC, EE (utility model), ES, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK (utility model), SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/069969 A1

(54) Title: A PROCESS FOR THE MANUFACTURE OF PHARMACEUTICAL TABLETS CONTAINING PAROXETINE HYDROCHLORIDE ANHYDRATE

(57) Abstract: Pharmaceutical tablets containing crystalline paroxetine hydrochloride anhydrate are prepared using a process comprising an initial wet granulation process in which an aqueous granulation liquid is added to a mixture of said anhydrate an excipients under high-shear conditions and the thus obtained wet granules are dried using a fluidized bed technique to obtain a water activity within a specified range, after which the dried granules after addition of further adjuvants are compressed into stable tablets each having an identical composition.

A process for the manufacture of pharmaceutical tablets containing paroxetine hydrochloride anhydrate

Field of the invention

The present invention is related to the manufacture of a pharmaceutical formulation for oral administration of paroxetine, which is a well-known drug having found widespread application in the treatment and prophylaxis of depression, anxiety, and several other disorders.

Background of the invention

The generic name paroxetine covers the compound (-)-trans-4-(4'-flourophenyl)-3-(3',4'-methylene-dioxyphenoxymethyl)-piperidine which is a liquid base most conveniently handled in the form of an acid addition salt.

According to EP 0 223 403 B1, the hydrochloride of a basic compound is in general the preferred salt for therapeutical use because of its physiological acceptability.

Paroxetine hydrochloride exists in amorphous as well as crystalline forms. Several crystalline forms have been reported. Thus, WO 96/94595 describes four new forms. Furthermore, the hydrochloride forms quite stable solvates comprising organic solvents as well as at least one hydrate.

According to the above EP 0 223 403 B1, paroxetine hydrochloride hemihydrate is a relatively stable compound, from which the bound water, however, may be removed to give the anhydrous form when subjected to extreme dessication conditions. Said patent specification also discloses that paroxetine hydrochloride anhydrate when compressed is partly converted into the hemihydrate even in a relatively dry environment.

WO 95/16448 discloses that a pink discolouration had been experienced as a problem when aqueous granulation processes were used in connection with the tablet formulation of the hydrochloride hemihydrate. It also discloses that the hemihydrate may be formulated into tablets by using a process in which water is absent, such as by direct compression or by dry granulation, and that the tablets thus produced are less likely to develop a pink hue.

According to WO 99/58113 claiming priority from 13 May 1998, all paroxetine hydrochloride sold before that date has been in the form of tablets containing the hemihydrate, but it is possible to formulate the hydrochloride anhydrate into tablets without conversion into the hemihydrate provided that extremely dry conditions are used in a tableting process in which a completely dry granulation is used or in which the tablets are pressed directly from the powdery dry constituents, i.e. that essentially anhydrous excipients must be used.

In said WO 99/58113, the partial conversion of the hydrochloride anhydrate into the hydrochloride hemihydrate during the tableting process is described as creating difficulties in establishing and maintaining a reference standard for regulatory and quality control purposes.

However, formulation processes avoiding hemihydrate formation by using dry granulation or dry direct tablet pressing have certain drawbacks.

Thus, there is a risk of segregation of the mixture of the active paroxetine salt and the various adjuvants during the conveyance of the mixture from the blending device to the tablet matrix. This involves a risk that the tablets produced have a nonuniform content of active drug and/or that non-desired varia-

tions occur as to mechanical properties or solubility and release of the active component.

Furthermore, the granulation and pressing operations performed as "dry" processes involve application of a higher pressure than necessary when a wet granulation process is used, which higher pressure increases the risk for the paroxetine hydrochloride anhydrate being converted into another crystalline form or partially into hemihydrate thereby creating an uncertainty as to the actual composition of the final tablet.

In contrast to tablet manufacturing using wet granulation in which fine particles and dust are bound into the granules, the dry processes are dusting, and due to the etching character of paroxetine hydrochloride this necessitates extensive provisions to avoid respiratory health risks to the staff.

Summary of the invention

The present invention is based on the recognition that it is possible to produce stable tablets containing crystalline paroxetine hydrochloride anhydrate by an alternative process which does not exhibit the drawbacks of the above tablet manufacturing processes using dry granulation or direct powder pressing.

Thus, it has turned out that tablets containing crystalline paroxetine hydrochloride anhydrate can be produced using a wet granulation method without conversion of the anhydrate into hemihydrate provided that a very fast drying of the granules is applied. Such fast drying is achieved by performing the drying in a process in which the material to be dried is fluidized in the drying air.

The process of the invention is characterized in the following steps:

- subjecting crystalline paroxetine hydrochloride anhydrate together with adjuvants comprising filler, disintegrant, binder, and water to a high-shear mixing operation,
- continuing the mixing to granulate the resulting mixture,
- fluidizing the resulting granulate in a flow of heated drying air to dry the granulate,
- continuing this drying until the water activity of the granulate has been reduced to 0.10-0.25 aw, when measured as described herein,
- optionally adding one or more further adjuvants,
- mixing a glidant into the granulate and,
- compressing the resulting mixture into tablets each having a pre-determined content of paroxetine hydrochloride anhydrate.

The term "glidant" is used herein in a broad sense also comprising adjuvants sometimes termed lubricants and agents improving the free flowing capability of the granulate.

By a preferred embodiment of the process, at least a part of the binder and at least a part of the water is added to a mixture of paroxetine hydrochloride anhydrate, filler, and disintegrant as an aqueous binder solution while said mixture is subjected to high-shear mixing.

Alternatively, a binder may as a dry material be included in the mixture of the paroxetine hydrochloride anhydrate, filler, and disintegrant, and the water added slowly to this mixture during mixing in a high-shear blender. However, a more efficient and faster dispersion of the binder on all particles forming the mixture is obtained when the binder is supplied dissolved in the aqueous granulation liquid.

The drying of the granulate while fluidized in the drying air may be performed using a conventional fluid bed dryer. As mentioned, the granulate is dried to a water activity between 0.10 and 0.25 aw. This means that the drying is more extensive than what is customary in connection with wet granulation as pre-treatment of materials to be compressed into tablets.

The water activity indicated here and in the attached claims is the one which is determined by using a device available from Novasina using the following procedure: Approximately 7 g granulate is placed in a chamber having a volume of approximately 20 ml. The chamber is sealed air-tight and kept at ambient temperature (20-25° C) for 30 min. The relative humidity of the air in the chamber is then recorded. The water activity of the granulate, expressed in the unit aw, is 1/100 of the relative humidity recorded for the air.

Preferably, the drying is continued until a water activity between 0.15 and 0.22 aw.

Even if the material is thus more dry than usual in tablet manufacture using wet granulation, the compression into tablets may be performed using less pressure than necessary in dry granulation or direct granulation processes. This is probably due to the fact that the binder is much better distributed than in said two processes.

The process of the invention may be performed using adjuvants and excipients of the type conventional when manufacturing tablets using a wet granulation pre-treatment.

A suitable filler may thus comprise one or more of the following substances: microcrystalline cellulose, mannitol, calcium phosphates, lactose, starch, sorbitol, and suchrose.

In view of the teaching of WO 99/58113, cited above, that microcrystalline cellulose shall preferably be avoided in paroxetine hydrochloride anhydrate tablets, it is surprising that in the present process microcrystlaline cellulose acts as a perfect adjuvant.

A suitable disintegrant may comprise one or more of the following substances: sodium starch glycolate, starch, gelatinated starch, crosprovidone, and micro crystalline cellulose.

A suitable binder comprises one or more of the following substances: polyvinyl pyrrolidone, gelatine, starch, methyl cellulose, hydroxypropylcellulose and copovidone.

A suitable glidant comprises one or more of the following substances: anhydrous colloidal silica, sodium stearyl fumarate, magnesium stearate, talc powder, and polyethylene glycol.

Very satisfactory results have been obtained using an embodiment wherein paroxetine hydrochloride anhydrate, mannitol, microcrystalline cellulose and sodium starch glycolate are subjected to high-shear mixing and simultaneously an aqueous solution of copovidone (Kolidon VA64) is added slowly and the mixing continued to obtain the desired granulation.

In this embodiment, the aqueous solution and, if necessary, further water are added in such an amount that a moisture content in the granulated mixture of 10-30% by weight is achieved before the drying is initiated. When other excipients are used, a moisture content outside these limits may be suitable.

An important feature is that this moisture is removed by a fast drying to avoid conversion of the paroxetine hydrochloride anhydrate into the hemihydrate.

The fluid bed drying may be performed as a continuos process or, preferably, batch-wise.

The drying periode shall preferably not exceed 3 h. It is more preferably less than 2 h and most preferably between 15 min. and 1 h.

Tablets produced by the present process have been stored for several months after which no detectable conversion of the crystalline paroxetine hydrochloride anhydrate had occurred. No hemihydrate was found and no conversion into other crystalline forms than the one of the starting material was detected.

Also the mechanical stability of the tablets was satisfactory. The crystalline hydrochloride anhydrate is reported as being hygroscopic. However, due to the fact that the paroxetine salt only constitutes a minor portion of the tablets, the hygroscopicity has no adverse effect on the stability and keeping qualities of the tablets when kept in normal air-tight containers or blister packings.

Preferably, the total weight of the tablets is between 100 and 750 mg and each contains from 10 to 60 mg paroxetine, calculated as the free base.

Analysis of the tablets indicated substantially the same content of paroxetine in each tablet, reflecting that no segregation had occurred during drying and compression operations.

As mentioned the tablets produced according to the invention show no tendency of discolouration during storing. However, since paroxetine has an unpleasant taste, it is preferred to subject the tablets to a film coating process. Such coating is not necessary to avoid discolouration or to secure sufficient stability of the tablets.

The binder in such a film coating may be methylhydroxypropyl cellulose, and water is used as solvent.

In contrast to what should be expected based on the teaching of the above cited prior art, also this contact between the crystalline paroxetine hydrochloride anhydrate and water takes place without conversion of the anhydrate into the hemihydrate.

Detailed description of the invention

In the following, the process of the invention is further elucidated by means of an embodiment example.

Example

22.22 kg crystalline paroxetine hydrochloride anhydrate, 80.0 kg microcrystalline cellulose PH101, 6.0 kg sodium starch glycolate, and 72.0 kg mannitol were introduced into a high-shear blender. After mixing of said four components in dry condition, an aqueous solution of 8.0 kg copovidone (Kolidon VA64) in 48.0 kg purified water was added slowly and the high-shear mixing continued to finish the granulation process.

The thus produced wet granulate was immediately transferred to a fluidized bed dryer and dried therein to a water activity of approximately 0.20 aw. The time period necessary to achieve this drying had been determined previously by guiding experiments. With the above stated composition of the wet granulate, the desired reduction of the water activity was obtained after drying in 1 h.

Subsequently, the dried granulate was sieved to remove lumps and afterwards transferred into a cone blender and therein mixed with 47.7 kg micro crystalline cellulose PH102, 0.48 kg anhydrous colloidal silica and 3.6 kg sodium stearyl fumarate.

The resulting dry mixture of granulate and said further adjuvants was compressed into tablets using a conventional rotary press having 16 pressing stations.

The pressing operation was carried out using a pressure lower than the one required in connection with direct powder pressing or pressing after dry granulation of similar materials. In spite thereof, the tablets were hard and had fine mechanical properties.

A total of 240 kg tablets, corresponding to 1 mio. pieces of tablets was produced, each comprising the same amount of crystalline paroxetine hydrochloride anhydrate, corresponding to 20 mg of the paroxetine base.

The tablets were film-coated using a coating liquid containing 1.382 kg methylhydroxypropyl cellulose (5), 0.806 kg micronized talc, 0.288 kg titanium dioxide and 26.324 kg purified water.

The tablets thus produced were subjected to several tests.

Stability studies of tablets packed in Al/PVC blister cards or polyethylene containers have been performed with satisfactory results. Also breakability studies have been performed.

Comparative dissolution tests have been made. The results show that more than 80% of the paroxetine is released from the film coated tablets within 10 min.

XRD studies have been performed on the finished product in order to confirm that no conversion of the crystalline paroxetine hydrochloride anhydrate to hemihydrate form takes place during manufacture and storage.

Also enantiomeric purity has been investigated. The results show that the content of (+)-paroxetine hydrochloride corresponds to less than 0.1% of the

paroxetine hydrochloride content, meaning that the finished product is enantiomerically pure.

In bioavailability studies tablets produced as above and also similar tablets having a paroxetine content of 40 mg, were after coating compared with commercially available film coated tablets containing paroxetine hydrochloride hemihydrate and found bio-equivalent to these.

It was also observed that the tablets, whether coated or not, did not show any discolouration even after prolonged storage.

PATENT CLAIMS

1. A process for the manufacture of pharmaceutical tablets containing paroxetine hydrochloride anhydrate, characterized in subjecting crystalline paroxetine hydrochloride anhydrate together with adjuvants comprising filler, disintegrant, binder, and water to a high-shear mixing operation,

- continuing the mixing to granulate the resulting mixture,
- fluidizing the resulting granulate in a flow of heated drying air to dry the granulate,
- continuing this drying until the moisture content of the granulate has been reduced to such an extent that the water activity of the granulate is between 0.10 and 0.25 aw, when measured as described herein,
- optionally adding one or more further adjuvants,
- mixing a glidant into this granulate, and
- compressing the resulting mixture into tablets each having a pre-determined content of paroxetine hydrochloride anhydrate.

2. A process according to claim 1, wherein at least a part of said binder and at least a part of said water is added as an aqueous binder solution to a mixture of paroxetine anhydrate chloride, filler and disintegrant while said mixture is subjected to high-shear mixing.

3. A process according to claim 1 or 2, wherein the granulate is dried to a water activity between 0.15 and 0.22 aw.

4. A process according to anyone of the preceding claims, wherein the filler comprises one or more of the following substances: microcrystalline cellulose, mannitol, calcium phosphates, lactose, starch, sorbitol, and succhrose.

5. A process according to anyone of the preceding claims, wherein the disintegrant comprises one or more of the following substances: sodium starch glycolate, starch, gelatinated starch, crospovidone, and micro crystalline cellulose.

6. A process according to anyone of the preceding claims, wherein the binder comprises one or more of the following substances: polyvinyl pyrrolidone, gelatine, starch, methyl cellulose, hydroxypropylcellulose and copovidone.

7. A process according to anyone of the preceding claims, wherein crystalline paroxetine hydrochloride anhydrate, mannitol, microcrystalline cellulose and sodium starch glycolate are subjected to high-shear mixing and simultaneously an aqueous solution of copovidone is added slowly to obtain the desired granulation.

8. A process according to claim 7, wherein said aqueous solution and, if necessary, further water, are added in such an amount that a moisture content in the granulated mixture of 10-30% by weight is obtained.

9. A process according to anyone of the above claims, wherein the tablets produced each has a weight between 100 and 750 mg and each contains from 10 to 60 mg paroxetine, calculated as the free base.

10. A process according to anyone of the preceding claims, wherein the tablets formed by the compressing are subjected to a coating operation using an aqueous coating liquid.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 August 2001 (16.08.2001)

PCT

(10) International Publication Number
WO 01/58449 A1

(51) International Patent Classification[7]: A61K 31/445, 9/14, 9/10

(21) International Application Number: PCT/GB01/00569

(22) International Filing Date: 9 February 2001 (09.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0003232.6 11 February 2000 (11.02.2000) GB

(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM PLC** [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **AL-GHAZAWI, Ahmad, Khalaf, Al-Deeb** [JO/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **ELDER David, Philip** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **MENEAUD, Padma** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: **WEST, Vivien**; SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/58449 A1

(54) Title: WATER DISPERSIBLE FORMULATION OF PAROXETINE

(57) Abstract: A water-dispersible formulation of paroxetine for immediate oral administration comprises a dry blend of paroxetine, a water-soluble dispersing agent, and a taste-masking agent, as a dispersible powder or moulded into a tablet.

WATER DISPERSIBLE FORMULATION OF PAROXETINE

The present invention relates to a novel composition containing a pharmaceutically active compound, and to the use of the composition in therapy. In particular, this invention is concerned with a formulation of paroxetine that is dispersible in water.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US-A-3912743 and US-A-4007196. An especially important compound among those disclosed is paroxetine, the (-)*trans* isomer of 4-(4'-fluorophenyl)-3-(3',4'-methylenedioxy-phenoxymethyl)-piperidine. This compound is used in therapy as the hydrochloride salt for the treatment and prophylaxis of *inter alia* depression, obsessive compulsive disorder (OCD) and panic.

Paroxetine hydrochloride has been described in the literature as a crystalline hemihydrate (see EP-A-0223403 of Beecham Group) and as various crystalline anhydrate forms (see WO96/24595 of SmithKline Beecham plc). These known forms are not ideally suited for all pharmaceutical applications because the known solid forms of paroxetine hydrochloride are relatively insoluble and are slow to dissolve completely.

However, for some patients swallowing a tablet can be difficult, whereas swallowing liquified medication is more easily carried out.

The present invention aims to satisfy the need for a liquid formulation of paroxetine hydrochloride. This achieved by providing a solid paroxetine formulation which is dispersible in water or an aqueuos medium for immediate administration, thus avoiding the need to store solutions or dispersions with risk of hydrolysis.

According to one aspect of the invention there is provided a dry blend of paroxetine, a water-soluble dispersing agent and a taste-masking agent.

The reference to paroxetine includes all forms of the compound in which paroxetine is available as a therapeutically effective agent. This includes paroxetine free base and pharmaceutically acceptable salts of paroxetine, especially paroxetine hydrochloride, particularly as the hemihydrate or one of the anhydrate forms.

The composition may be in powder form, especially with one or more conventional excipients, such as diluents, flavouring agents and sweeteners. Preferably a powder form

is supplied as sealed sachets of the powder containing a unit dose of paroxetine. Alternatively the powder may be loaded into capsule shells, which are broken to add the powder to an aqueous carrier.

The composition may also be provided as a shaped composition such as a tablet, in which case the composition typically includes one or more conventional excipients for tablet formation, such as mould lubricants and disintegrants. Tablets may be formulated to disintegrate in water, for dispersion as a suspension for swallowing by drinking, or as bite-dispersion tablets which are broken in the mouth by biting and dispersed in saliva for swallowing.

Suitable dispersing agents include polyvinyl pyrrolidone (such as Crospovidone XL, from ISP International Corp), calcium carbonate (such as Cal-Carb, from Whittaker, Clark & Daniels), and sodium starch glycolate (such as Explotab, from Edward Mendell Co Inc). These are incorporated into the formulation, singularly or in combination, to disperse the active ingredient in water after break-up of a tablet or addition of a powder to water, and to maintain the active ingredient in a dispersed form.

Because of the bitter taste of paroxetine, when paroxetine is administered in a dosage form which is not swallowed whole, it is in practical terms essential that the composition also incorporates a taste masking agent to assist in patient compliance. Suitable taste masking agents includes potassium form polyacrylic acid ion exchange resins (such as Polacrilin K, from Rohm & Haas), β-cyclodextrin (such as Kleptose, from Roquette Inc), lecithin (such as Epikuron, from Lucas Meyer) and methacrylic acid copolymers (such as Eudragit L30D55, from Rohm & Haas).

The taste masking agents typically act by the formation of either an ion-exchange resin, inclusion complex, encapsulation or coating of the drug, to assist the patient to comply fully with the medication regime by swallowing the whole of the liquid dispersion.

Alternatively the taste masking agent may be an intense sweetener, such as those derived from fruit flavanoids.

The relative quantities of the dispersing agents may be adjusted to satisfy the desired balance of dispersability and taste masking. Also, the amount of dispersing agents relative to the other tableting excipients may be adjusted to suit the desired requirements for the rate of break-up of the tablet in water.

* equivalent to 20mg paroxetine free base

Example 4

	mg/tab
Paroxetine hydrochloride hemihydrate*	22.76
β-Cyclodextrin	68.40
Citric Acid	5.00
Polyvinylpyrrolidone	25.00
Calcium Carbonate	25.00
Flavour	25.00
Sweetener	25.00
Microcrystalline Cellulose	51.34
Magnesium Stearate	2.50
Total	250.00

* equivalent to 20mg paroxetine free base

Example 5

	mg/tab
Paroxetine hydrochloride hemihydrate*	22.76
β-Cyclodextrin	68.40
Citric Acid	5.00
Polyvinylpyrrolidone	25.00
Calcium Carbonate	15.00
Flavour	25.00
Sweetener	25.00
Xylitol	51.34
Sodium Starch Glycolate	10.00
Magnesium Stearate	2.50
Total	250.00

* equivalent to 20mg paroxetine free base

Example 6

	mg/tab
Paroxetine hydrochloride hemihydrate*	22.76
Lecithin	45.52
Citric Acid	5.00
Polyvinylpyrrolidone	25.00
Calcium Carbonate	25.00
Flavour	25.00
Sweetener	25.00
Microcrystalline Cellulose	74.22

Typical excipients to make up the balance of the tablet formulation and to provide the requisite moldability and integrity of the tablet structure are conventional additives such as magnesium stearate and microcrystalline cellulose. The tablet may also contain sweeteners and flavourings to adjust the desired taste characteristics.

For use as a powder, the paroxetine, dispersing and taste masking agents may be blended as powders with other excipients such as solid diluents, flow control agents and desiccants, and then loaded into sachets or capsule shells by conventional means.

In an alternative procedure, the paroxetine is dispersed in a solution of a capsulateing material and spray dried before blending with other excipients for tabletting or filling powder containers.

The paroxetine hydrochloride used in this invention is preferably in the form of the crystalline hemihydrate (see EP-A-0223403). However other crystalline forms may also be used such as crystalline anhydrates (see WO96/24595), and other salts such as the maleate and acetate (see US-A-3912743 and US-A-4007196).

Therapeutic uses of the paroxetine composition of this invention include treatment of alcoholism, anxiety, depression, obsessive compulsive disorder, panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, pre-menstrual syndrome (PMS), adolescent depression, trichotillomania, dysthymia, and substance abuse, referred to below as "the Disorders".

Accordingly, the present invention also provides:

the use of a composition of this invention for the treatment or prophylaxis of one or more of the Disorders; and

a method of treating one or more of the Disorders which comprises administering a composition of this invention to a person suffering from one or more of the Disorders.

The present invention is illustrated by the following Examples.

Example 1

	gm
Paroxetine chloride hemihydrate	22.80
Polacrilin Potassium	40.00
Polyvinyl Pyrrolidone	25.00
Sweetener	12.00
Flavourings	27.00
Magnesium stearate	2.50
Microcrystalline Cellulose	120.70
	250.00

The 250 g batch of the above materials were sieved, blended, and then subjected to compression in tablet moulds to form approx. 1000 tablets of approx. 250 mg.

Similarly, tablets were prepared from the formulations in Examples 1-7

Example 2

	mg/tab
Paroxetine hydrochloride hemihydrate*	22.76
Polacrilin Potassium	45.52
Citric Acid	5.00
Polyvinylpyrrolidone	25.00
Calcium Carbonate	25.00
Flavour	25.00
Sweetener	25.00
Microcrystalline Cellulose	74.22
Magnesium Stearate	2.50
Total	250.00

* equivalent to 20mg paroxetine free base

Example 3

	mg/tab
Paroxetine hydrochloride hemihydrate*	22.76
Polacrilin Potassium	45.52
Citric Acid	5.00
Polyvinylpyrrolidone	25.00
Calcium Carbonate	15.00
Flavour	25.00
Sweetener	25.00
Xylitol	74.22
Sodium Starch Glycolate	10.00
Magnesium Stearate	2.50
Total	250.00

Magnesium Stearate	2.50
Total	250.00

* equivalent to 20mg paroxetine free base

Example 7

	mg/tab
Paroxetine hydrochloride hemihydrate*	22.76
Lecithin	45.52
Citric Acid	5.00
Polyvinylpyrrolidone	25.00
Calcium Carbonate	15.00
Flavour	25.00
Sweetener	25.00
Xylitol	74.22
Sodium Starch Glycolate	10.00
Magnesium Stearate	2.50
Total	250.00

* equivalent to 20mg paroxetine free base

Example 8

	gm
Paroxetine hydrochloride hemihydrate*	22.76
Methacrylic Acid Copolymer Type C	1.14
Talc	0.35
Triethyl Citrate	0.14
Citric Acid	5.00
Polyvinylpyrrolidone	25.00
Calcium Carbonate	25.00
Flavour	25.00
Sweetener	25.00
Microcrystalline Cellulose	118.11
Magnesium Stearate	2.50
Total	250.00

* equivalent to 20mg paroxetine free base

A suspension in water of paroxetine, methacrylic acid copolymer, talc and triethyl citrate from the above formulation was spray dried . The spray dried material and remaining excipients were sieved, blended, and then subjected to compression in tablet moulds to form approx. 1000 tablets of approx. 250mg

Example 9

	mg/tab
Paroxetine hydrochloride hemihydrate*	22.76
Methacrylic Acid Copolymer Type C	1.14
Talc	0.35
Triethyl Citrate	0.14
Citric Acid	5.00
Polyvinylpyrrolidone	15.00
Calcium Carbonate	25.00
Flavour	25.00
Sweetener	25.00
Xylitol	118.11
Sodium Starch Glycolate	10.00
Magnesium Stearate	2.50
Total	250.00

* equivalent to 20mg paroxetine free base

Using the procedure of Example 8, tablets were prepared from the above formulation.

CLAIMS

1. A pharmaceutical composition which is a dry blend of :
paroxetine hydrochloride, another pharmaceutically acceptable salt of paroxetine, or paroxetine free base;
a water-soluble dispersing agent; and
a taste-masking agent.

2. A composition according to claim 1 which is in powder form.

3. A composition according to claim 1 which is a shaped composition including one or more conventional excipients for tablet formation.

4. A composition according to claim 1, 2 or 3 in which the dispersing agent is selected from polyvinyl pyrrolidone, calcium carbonate and sodium starch glycolate.

5. A composition according to claim 1, 2, 3 or 4 in which the taste masking agent is an intense sweetener.

6. A composition according to claim 5 in which the taste masking agent is selected from potassium form polyacrylic acid ion exchange resins, β-cyclodextrin, lecithin and methacrylic acid copolymers.

7. Use of a composition according to any one of claims 1 to 6 for the treatment or prophylaxis of one or more of the Disorders.

8. Method of treating one or more of the Disorders which comprises administering a composition according to any one of claims 1 to 6 to a person suffering from one or more of the Disorders

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/445, 9/14

A1

(11) International Publication Number: **WO 99/48499**

(43) International Publication Date: 30 September 1999 (30.09.99)

(21) International Application Number: PCT/GB99/00922

(22) International Filing Date: 24 March 1999 (24.03.99)

(30) Priority Data:
9806312.6 24 March 1998 (24.03.98) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TX8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CRAIG, Andrew, Simon [GB/GB]; Smithkline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). WARD, Neal [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB).

(74) Agent: GIDDINGS, Peter, John; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PAROXETINE COMPOSITIONS

(57) Abstract

Paroxetine is adsorbed on a carrier to form a free-flowing powder useful for capsule filling or for tablet formation; and used in therapy to treat depression.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PAROXETINE COMPOSITIONS

The present invention relates to new formulations of a pharmaceutically active compound, and in particular to a novel formulation of paroxetine.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US-A-3912743 and US-A-4007196. An especially important compound among those disclosed is paroxetine, the (-)*trans* isomer of 4-(4'-fluorophenyl)-3-(3',4'-methylenedioxy-phenoxymethyl)-piperidine.

In the literature this compound is usually isolated as an acid salt, especially the hydrochloride. Paroxetine is approved for human use as the hydrochloride salt, and has been proposed for the treatment and prophylaxis of *inter alia* depression, obsessive compulsive disorder (OCD) and panic.

Paroxetine hydrochloride has been described in the literature as a crystalline hemihydrate (see EP-A-0223403 of Beecham Group) and as various crystalline anhydrate forms (see WO96/24595 of SmithKline Beecham).

Paroxetine free base has hitherto been disclosed in the literature as an oil, and so the free base has not itself been considered for therapeutic use, preference being given to crystalline forms which can be more easily purified and processes into dosage forms.

The present invention is based on the discovery that paroxetine, for example paroxetine free base, is advantageously formulated into pharmaceutical compositions when adsorbed on or absorbed by a solid carrier.

The present invention provides a composition comprising paroxetine or a pharmaceutically acceptable derivative thereof adsorbed on or absorbed by a pharmaceutically acceptable solid carrier, and the use of the composition as a therapeutic agent or for the manufacture of a medicament.

By this invention paroxetine may be obtained as a free-flowing powder that can be used directly (for example by direct compression into tablet form) or with further compounding ingredients in therapy.

The paroxetine used in carrying out this invention is preferably paroxetine free base, but may alternatively be a pharmaceutically acceptable derivative such as a salt, more especially the hydrochloride.

The composition of this invention is simply obtained by combining a solution of paroxetine with a suitable adsorbent or absorbent material and evaporating the solvent, for example by spray drying. The solvent is suitably toluene, ethanol, acetone, propan-2-ol, or ethyl acetate, or any other suitable solvent or mixture of solvents, in a paroxetine concentration of between 1 and 20%, more preferably between 1 and 4%.

Alternatively an oil obtained by removal of solvent from a solution may be blended with a solid adsorbent or absorbent material.

Typically the material selected as carrier for the paroxetine is an excipient suitable for tablet formation or as a fill material for gelatine capsules, such as cyclodextrin (beta and /or gamma), porous silicates, starch, lactose or calcium phosphate, silica, sorbitol, maltodextrin, microcrystalline or powdered cellulose, sodium or calcium carboxymethylcellulose, calcium carbonate, kaolin, magnesium aluminium silicate. Additionally, soluble excipients such as magnesium stearate may form part of the solution phase.

Advantageously the carrier is one that also has a taste-masking effect, for example ion-exchange resins.

A solution of paroxetine free base may be prepared by addition of a base such as triethylamine to a solution of a crystalline paroxetine salt especially the hydrochloride or acetate. Alternatively the solution may be prepared by basifying a solution of an

amorphous paroxetine hydrochloride or a crystalline anhydrate or hydrated form of paroxetine hydrochloride.

The preparation of the free base and the maleic acid salt are described in Example 2 of US 4007196. The acetate salt may also be used as a starting material. Procedures for forming salts are described in EP-A-0223403.

Additionally the paroxetine free base may be prepared as a solution or oil by adding a base such as potassium hydroxide to a solution of a N-protected paroxetine compound such as N-phenoxycarbonyl paroxetine.

The composition of this invention comprising paroxetine adsorbed on or absorbed by a solid carrier may be formulated with or without conventional excipients for tablet formation or used as a powder fill for capsules.

The amount of paroxetine used is adjusted such that in a single unit dose there is a therapeutically effective amount of paroxetine. Preferably the unit dose contains from 10 to 100 mg paroxetine (as measured in terms of the free base). More preferable the amount of paroxetine in a unit dose is 10mg, 20mg, 30mg, 40mg or 50mg. The most preferred amount of paroxetine in a unit dose is 20mg.

Therapeutic uses of the paroxetine product of this invention include treatment of: alcoholism, anxiety, depression, obsessive compulsive disorder, panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, pre-menstrual syndrome (PMS), adolescent depression, trichotillomania, dysthymia, and substance abuse, referred to below as "the disorders".

Accordingly, the present invention also provides:

a pharmaceutical composition for treatment or prophylaxis of the disorders comprising paroxetine or a pharmaceutically acceptable derivative thereof adsorbed on or absorbed by a solid carrier and, optionally, at least one further pharmaceutically acceptable excipient;

the use of paroxetine or a pharmaceutically acceptable derivative thereof adsorbed on or absorbed by a solid carrier to manufacture a medicament for the treatment or prophylaxis of the disorders; and

a method of treating the disorders which comprises administering an effective or prophylactic amount of paroxetine or a pharmaceutically acceptable derivative thereof adsorbed on or absorbed by a solid carrier to a person suffering from one or more of the disorders.

The invention is illustrated by the following Examples:

Example 1. Preparation of tablet pre-mix containing paroxetine free base.

A mixture of dibasic calcium phosphate dihydrate (408 g), hydroxypropylmethyl cellulose (25 g) and sodium starch glycollate (25 g) was blended in a key granulator for 3 minutes at a stir rate of 240 r.p.m. and an impeller rate of 3000 r.p.m. Purified water (57 ml) was added at a rate of approximately 4 ml/minute for 13.5 minutes while the key granulator was set at a stir rate of 240 r.p.m. and the impeller rate was set at 1500 r.p.m. The mixture was stirred for a further 1 minute, and the resulting granules dried in an air oven at 50°C for 3 hours.

A portion of the granules prepared above (50 g) was added to a solution of paroxetine free base (2.0 g) in propan-2-ol (50 ml) and the resulting slurry dried under vacuum with agitation at 50°C.

This product is suitable for direct compression into tablets containing 10, 20, or 30 mg paroxetine.

Example 2. Preparation of a solid supported form of paroxetine free base.

A stirred mixture of N-phenoxycarbonyl paroxetine (50.0g), potassium hydroxide (45.0g) and toluene (750ml) was heated to reflux under a nitrogen atmosphere for 3 hours. After allowing the mixture to cool to room temperature, distilled water (500ml) was added and the mixture stirred for 30 minutes. The organic layer was separated, dried over magnesium sulfate and concentrated to a total volume of 85ml.
Toluene (100ml) was added to an aliquot of the solution of paroxetine free amine in toluene (0.43g/ml) (2.4 ml) and to this solution was added Celite (25.0g) and

the mixture stirred for 5 minutes. Solvent was removed under reduced pressure (water bath 55°C) to afford the Celite supported paroxetine free amine as a free moving powdery solid (26.0g).

This product may be mixed with additional excipients and compressed into tablets or added directly to capsule shells to make a product containing a therapeutic dose of paroxetine.

Example 3

Spray drying of paroxetine hydrochloride solution onto a suspended carrier material.

Anhydrous paroxetine hydrochloride (60 g) was dissolved in anhydrous ethanol (725 ml) and the clear solution slurried with maltodextrin DE4-6 (506 g). The uniform suspension was spray-dried in a Niro Mobile Minor (TM) closed cycle spray dryer using nitrogen as the process gas, a rotary atomiser wheel spinning at 27,000 r.p.m. (alternatively a co-current or fountain two-fluid nozzle could be used), an inlet temperature of 96-104 C and outlet temperature of 44-50 C at a feed rate of 4.1 kg per hour. A white free-flowing product was recovered (490 g) which was found to have a mean particle size of 84 microns.

Example 4

Preparation of tablet pre-mix containing paroxetine hydrochloride.

A mixture of dibasic calcium phosphate dihydrate (408 g), hydroxypropylmethyl cellulose (25 g) and sodium starch glycollate (25 g) was blended in a key granulator for 3 minutes at a stir rate of 240 r.p.m. and an impeller rate of 3000 r.p.m. Purified water (57 ml) was added at a rate of approximately 4ml/minute for 13.5 minutes while the key granulator was set at a stir rate of 240 r.p.m. and the impeller rate was set at 1500 r.p.m. The mixture was stirred for a further 1 minute, and the resulting granules dried in an air oven at 50°C for 3 hours.

A solution of paroxetine hydrochloride hemihydrate (2.0 g) in ethanol (100 ml) was added to the granules prepared above (50 g) and the slurry dried under vacuum at 50°C.

Example 5

Preparation of tablet pre-mix containing paroxetine hydrochloride.

A solution of paroxetine hydrochloride hemihydrate (2.0 g) in ethanol (150 ml) was added to celite (50 g), the mixture stirred and the slurry dried under vacuum at 50°C to afford a free moving powdery solid, suitable for use as a component of a tablet or capsule formulation.

Example 6

Preparation of tablet pre-mix containing paroxetine hydrochloride.

A stirred mixture of N-phenoxycarbonyl paroxetine (50.0 g), potassium hydroxide (45.0 g) and toluene (750 ml) was heated to reflux under a nitrogen atmosphere for 3 hours. After allowing the mixture to cool to room temperature, distilled water (500 ml) was added and the mixture stirred for 30 minutes. The organic layer was separated, dried over magnesium sulphate and filtered. An aliquot of this solution of paroxetine free amine in toluene [0.048 g/ml] (21.0 ml) was diluted with a further 30 ml of toluene and heated to 60°C. Concentrated hydrochloric acid (0.34 ml) was added and the mixture stirred for 10 minutes. Tablet granules (25.0g), prepared as in Example 4, were added and the mixture stirred at 60°C for 5 minutes. Solvent was removed under reduced pressure at 70°C to afford a mobile powdery solid (26.0g).

Example 7

Preparation of tablet pre-mix containing paroxetine hydrochloride.

Concentrated hydrochloric acid (0.34ml) was added to a stirred solution of paroxetine acetate (1.18g) in toluene (50ml) at 60°C and the mixture stirred for 10 minutes. Tablet granules (25.0g), prepared as in Example 4, were added and the mixture stirred at 60°C for 5 minutes. Solvent was removed under reduced pressure at 70°C to afford a free flowing powdery solid (26.0g).

CLAIMS

1. Paroxetine or a pharmaceutically acceptable derivative thereof adsorbed on or absorbed by a solid carrier.

2. A pharmaceutical composition comprising paroxetine or a pharmaceutically acceptable derivative thereof adsorbed on or absorbed by a solid carrier.

3. Use of paroxetine or a pharmaceutically acceptable derivative thereof adsorbed on or absorbed by a solid carrier to manufacture a medicament for the treatment of depression.

4. A method of treating depression which comprises administering an effective amount of paroxetine or a pharmaceutically acceptable derivative thereof adsorbed on or absorbed by a solid carrier to a person suffering from depression.

5. A composition of matter, use or method according to any preceding claim wherein the paroxetine is in the form of its free base.

6. A process for the preparation of a composition of matter according to claim 1, 2 or 5, which process comprises combining a solution of paroxetine or a pharmaceutically acceptable derivative thereof with the adsorbent or absorbent solid carrier material and evaporating the solvent.

7. A process according to claim 6, wherein the carrier material is suspended in the solvent prior to evaporation of the solvent.

8. A process according to claim 6, wherein the carrier material is dissolved in the solvent prior to evaporation of the solvent.

9. A process according to any one of claims 6 or 8, wherein the evaporation of the solvent is carried out by spray drying.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 December 2000 (28.12.2000)

PCT

(10) International Publication Number
WO 00/78288 A2

(51) International Patent Classification[7]: A61K 9/16, 31/4525, A61P 25/00

(21) International Application Number: PCT/GB00/02421

(22) International Filing Date: 22 June 2000 (22.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9914600.3 22 June 1999 (22.06.1999) GB

(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM P.L.C.** [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CRAIG, Andrew, Simon** [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). **JACEWICZ, Victor, Witold** [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB).

(74) Agent: **GIDDINGS, Peter, John**; SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/78288 A2

(54) Title: NOVEL PROCESS

(57) Abstract: Difficulties arising when spray drying paroxetine hydrochloride from water-containing solutions are overcome by keeping the outlet gas temperature in the range 40-55 °C, and the water content of the outlet gas below 1.1 kg per 100 kg of outlet gas. The feedstock may be a water-containing solution or suspension of excipient(s) in the range 20-60 % by wt. and paroxetine hydrochloride in the range 1-10 % by wt., in which case the outlet gas temperature is in the range 40-75 °C.

NOVEL PROCESS

The present invention relates to a process for the preparation of a pharmaceutically active compound in a form suitable for use of the compound in therapy. In particular this invention is concerned with the preparation of a free-flowing form of paroxetine hydrochloride by spray-drying.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US-A-3912743 and US-A-4007196. An especially important compound among those disclosed is paroxetine, the (-)*trans* isomer of 4-(4'-fluorophenyl)-3',4'-methylenedioxy-phenoxymethyl)-piperidine. This compound is used in therapy as the hydrochloride salt to treat *inter alia* depression, obsessive compulsive disorder (OCD) and panic.

In US patent 5,672,612 (Pentech) paroxetine hydrochloride is isolated by spray drying from anhydrous ethanol.

EP-810 224-A (Asahi) discloses as its preferred product paroxetine hydrochloride in anhydrous form, which is prepared by "spray drying virtually in the absence of water". The specification mentions the use of a wide range of solvents, one of which is water, but makes it clear that anhydrous alcohols, particularly anhydrous ethanol is preferred. Spray drying of dilute solutions is said to be necessary to produce a product with "good flowability". Only Example 5 describes spray drying from water, and it uses a very dilute (1%) solution. The product is "hydrous amorphous paroxetine hydrochloride". All the other Examples spray dry from anhydrous ethanol.

WO 98/31365 (SmithKline Beecham) discloses the use of aqueous and mixed aqueous organic solvents for spray drying paroxetine hydrochloride. The only example describes spray drying of an aqueous solution at 10% concentration.

Our practical experience of spray-drying paroxetine hydrochloride has brought to light a number of technical problems which must be solved to carry out spray-drying on a manufacturing scale.

Spray drying from dilute solutions is undesirable on economic grounds and tends to give a product with small particles and a large component of "fines".

It is difficult to remove residual solvents from amorphous materials, such as spray dried paroxetine hydrochloride, because of their glass-like supercooled liquid character. Since the process is intended as the final isolation step for the commercial manufacture of the drug substance, control of undesirable impurities, including solvents, is essential.

Totally anhydrous solvents, particularly absolute ethanol, are expensive and therefore undesirable on economic grounds. Cheaper anhydrous products contain undesirable impurities and denaturing agents.

Paroxetine hydrochloride readily forms solvates from alcoholic solvents such as propan-2-ol and ethanol. These solvates crystallise from solution at quite low concentration and prevent the use of concentrated feedstock for spray drying. Low concentration feedstock is undesirable on economic and environmental grounds; during spray drying from a solvent all the solvent is evaporated and mixed with a large volume of nitrogen gas (or other inert gas). This gas must be treated to remove the solvent efficiently and completely for environmental and safety reasons.

This invention provides procedures by which good quality free-flowing anhydrous amorphous paroxetine hydrochloride can be prepared on a manufacturing scale in excellent yield by an efficient process that uses high concentration feedstock and inexpensive, environmentally acceptable solvents, including 100% water. Previous attempts at spray drying paroxetine hydrochloride from water or water solvent mixtures have often resulted in unsatisfactory sticky products, which adhere to the apparatus and result in poor yields and poor flow characteristics. This invention is based on the finding that these problems can be solved by *inter alia* close control of the outlet temperature and outlet gas water content.

According to the present invention there is provided a process for spray drying paroxetine hydrochloride from water-containing solutions, in which the outlet gas temperature is in the range 40-55°C, preferably in the range 43-50°C, and the water content of the outlet gas is kept below 1.1 kg per 100 kg of outlet gas.

Typically the feedstock is a water-containing solution at a concentration of 5-50%, preferably 7-30% most preferably 10-25% by wt. paroxetine hydrochloride. The non-aqueous component of the solvent mixture may be propan-2-ol, ethanol, or acetone, or other inexpensive commercial grade solvents that are miscible with water without decreasing the solubility of paroxetine hydrochloride.

Preferably the solvent is pure water, in which case the spray drying preferably uses heated feedstock between 60 and 95°C and jacketed heated lines. The aqueous solutions typically contain 3-30% paroxetine hydrochloride in the feedstock

The spray drying may be carried out using pre-dried air, and typically using between 1 and 15 kg nozzle gas per kg feedstock

Spray drying may be followed by post drying in an air or vacuum oven or a fluidised bed drier.

The much greater specific heat of evaporation of water compared to other suitable solvents, means that spray drying conditions are mainly determined by the water component of a solvent mixture. For the purposes of calculation at low levels of water (less than 10%), non-aqueous solvents are treated as equivalent in effect to between one fifth and one tenth of their weight of water, according to their specific heat of evaporation.

The outlet gas temperature is suitably maintained in the range 40-55°C, preferably in the range 43-50°C. The water content of the outlet gas should be kept below 1.1 kg per 100 kg of outlet gas, hence the economics of the operation are improved if pre-dried air or nitrogen is used, particularly when spray drying from 100% aqueous solvent.

The drying gas inlet temperature is not of primary importance, since a suitable value is determined for a particular apparatus by other parameters, i.e. composition of the feedstock, inlet gas flow rate and humidity, and the critical parameters outlet gas temperature and water content. In practice, an inlet gas temperature in the range 70-100°C is found to be appropriate, though at less than optimum feed rates a lower inlet temperature may be necessary to keep the outlet temperature within the required range.

The maximum feed rate for the spray drier is determined by the feedstock composition, drying gas flow rate and humidity, and the acceptable outlet gas water content. Operation significantly below the maximum feed rate is undesirable on economic grounds, and results in an increase in the outlet gas temperature, which must be compensated to bring it within the specified range.

An essential requirement for successful spray dying paroxetine hydrochloride from water-containing solutions is that the product should have sufficient time in the drying chamber to satisfy the stated values for outlet gas temperature and water content of the outlet gas; effectively to reach a low enough water and solvent content to bring the glass temperature above that of the outlet gas. Various parameters have an effect on these values; the time available is determined by the construction and dimensions of the apparatus and the direction of the spray; the time required is determined by the water and solvent content of the outlet air and the droplet size of the spray. In the case of a two fluid nozzle, the droplet size can be adjusted by selection of a suitable nozzle, or by increasing the amount of nozzle gas. As much as 15 kg nozzle gas per kg feedstock may be necessary at high feedstock concentrations. In the case of an atomising wheel, the droplet size is controlled by the choice of wheel and the rotation rate. With either apparatus, a tendency towards stickiness can be corrected by reducing the droplet size.

A major economic and environmental disadvantage of previous methods for spray drying paroxetine hydrochloride has been the requirement for low concentration feedstock. We have found that high concentration feedstock may be prepared from water/solvent mixtures which are stable towards crystallisation (and hence blocking of tubes and nozzles) without the need for excessive heating. For example, a 5% solution of paroxetine hydrochloride in anhydrous propan-2-ol crystallises very readily and must be kept near to reflux temperature to ensure freedom from blockages. By contrast, addition of 5% water gives a solution that has no tendency to crystallise as the propan-2-ol solvate and is prevented from crystallising as the hemihydrate by gentle warming. At higher water content, for example between 30 and 60%, feedstock concentrations in excess of 30% can be achieved without excessive heating.

Despite the greater solubility of paroxetine hydrochloride in water/solvent mixtures, there are clear economic advantages to spray drying from water alone. For instance, air can be used in place of nitrogen gas or other inert gas, since there is no requirement for flameproof

operation, but is preferably pre-dried. Furthermore, there is no economic or environmental need to recover solvents or to scrub outlet gases. We have found that, provided the above-mentioned parameters are adhered to, economic spray drying from 100% aqueous solutions is entirely feasible. Optimal concentrations range from 10 to 30% paroxetine hydrochloride in the feedstock, though at the higher concentrations the solution must be maintained above 80°C at all times. This means that the design of the delivery system to the spray dryer desirably incorporates jacketed lines right up to the spray nozzle.

The product of spray drying from high concentration aqueous systems is a free-flowing white powder, suitable for formulation into pharmaceutical products, but to maximise throughput it may be desirable to tolerate a residual level of water or solvent. This residue may be removed by post drying in conventional drying ovens, but is most conveniently achieved by the use of a combined spray dryer/fluidised bed drier.

In another aspect of this invention a water or water/solvent solution of paroxetine hydrochloride is slurried with excipient(s) and then spray dried. The excipient(s) may be selected so that the product is suitable for direct formulation into tablets, capsules or other dosage forms with little or no further treatment. Typically, the slurry contains from 20 to 60% by weight of solid excipients, or in some cases excipients in solution. In the presence of excipients, it may be appropriate to maintain the amount of paroxetine hydrochloride in the range 1-10%. Suitable excipients include dibasic calcium phosphate dihydrate, hydroxypropylmethyl cellulose and/or sodium starch glycollate.

Slightly higher outlet gas temperatures, for example 5-20°C, may be used if the paroxetine hydrochloride is spray dried in the presence of a large excess of excipients.

Spray-dried paroxetine hydrochloride obtained using this invention has been found to be particularly suitable for applications where uniform particle size and good flow properties are advantageous. Furthermore as a result of the close control of particle size possible by spray-drying, the product may be handled conveniently and safely without the hazards associated with the dust produced when conventionally prepared paroxetine hydrochloride solids are prepared. Examples of applications where uniform particle size are advantageous include controlled release and microencapsulation (coated particle technology). Samples may be

produced with particle sizes for specific applications, for example in the range 10-1000 microns.

Microencapsulation may be incorporated into the spray-drying process or may be carried out in a subsequent step. This technology is useful for taste masking, rapid or controlled release formulations, hence control of pharmacokinetics including the matching of pharmacokinetic properties for combination products.

The spray-dried product of this invention may be formulated for therapy in the dosage forms described in EP-A-0223403 or WO 96/24595. The free-flowing properties are advantageous for the preparation of solid formulations. Also the easily soluble nature of spray dried paroxetine hydrochloride makes it suitable for the preparation of solutions for parenteral use.

Therapeutic uses of the paroxetine product of this invention include treatment of: alcoholism, anxiety, depression, obsessive compulsive disorder, panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, pre-menstrual syndrome (PMS), adolescent depression, trichotillomania, dysthymia, and substance abuse, referred to below as "the disorders".

Accordingly, the present invention also provides:

a pharmaceutical composition for treatment or prophylaxis of the disorders comprising paroxetine hydrochloride spray-dried in accordance with this invention and a pharmaceutically acceptable carrier or an aqueous solution of reconstituted paroxetine hydrochloride spray-dried in accordance with this invention;

the use of paroxetine hydrochloride spray-dried in accordance with this invention to manufacture a medicament in solid or reconstituted liquid form for the treatment or prophylaxis of the disorders; and

a method of treating the disorders which comprises administering an effective or prophylactic amount of paroxetine hydrochloride spray-dried in accordance with this invention as a solid oral composition or as a reconstituted aqueous oral or parenteral composition to a person suffering from one or more of the disorders.

The invention is illustrated by the following Examples

The compositions of the feed solutions/suspensions for the Examples are given as percentages or ratios by weight. The excipient used in these Examples was a blend of dibasic calcium phosphate dihydrate (89%), hydroxypropylmethyl cellulose (5.5%) and sodium starch glycollate (5.5%).

Example 1

A 5% solution of paroxetine hydrochloride hemihydrate in propan-2-ol/water (95:5) was spray dried under the following conditions:

Apparatus:	Niro Mobile Minor
Feed Temperature:	50-73°C
Feed Rate:	3.3 kg/hr
Nozzle diameter	1.5 mm
Nozzle Air/Feed Ratio:	0.9
Inlet Temperature:	90°C
Outlet Temperature:	43-44°C
Drying Nitrogen Flow:	88 kg/hr
Duration:	19 minutes
Product wt:	25.2 g
Appearance:	Free moving white powder

The product was placed in a vacuum oven at 40°C for 16 hours.

Example 2

A combined solution/slurry of paroxetine hydrochloride hemihydrate (2%) and excipient (23%) in propan-2-ol/water [95:5] was spray dried under the following conditions:

Apparatus:	Niro Mobile Minor
Feed Temperature:	64-68°C
Feed Rate:	5.7 kg/hr
Nozzle diameter	1.5 mm

Nozzle Air/Feed Ratio:	0.7
Inlet Temperature:	90°C
Outlet Temperature:	43-44°C
Drying Nitrogen Flow:	86 kg/hr
Duration:	11 minutes
Product wt:	208.9 g
Appearance:	Free moving white powder

The product was placed in vacuum oven at 40°C for 16 hours.

Example 3

A combined solution/slurry of paroxetine hydrochloride hemihydrate (2%) and excipient (23%) in ethanol/water [96:4] was spray dried under the following conditions:

Apparatus:	Niro Mobile Minor
Feed Temperature:	30-31°C
Feed Rate:	4.3 kg/hr
Nozzle diameter	2.0 mm
Nozzle Air/Feed Ratio:	0.9
Inlet Temperature:	90°C
Outlet Temperature:	42°C
Drying Nitrogen Flow:	89 kg/hr
Duration:	14 minutes
Product wt:	198.0 g
Appearance:	Free moving white powder

The product was placed in vacuum oven at 40°C for 16 hours.

Example 4

A combined solution/slurry of paroxetine hydrochloride hemihydrate (2%) and excipient (23%) in propan-2-ol/water [80:20] was spray dried under the following conditions:

Apparatus:	Niro Mobile Minor
Feed Temperature:	27-28°C
Feed Rate:	3.5 kg/hr
Nozzle diameter	2.0 mm
Nozzle Air/Feed Ratio:	1.4
Inlet Temperature:	90°C
Outlet Temperature:	40-42°C
Drying Nitrogen Flow:	88 kg/hr
Duration:	17 minutes
Product wt:	145.9 g
Appearance:	Free moving white powder

The product was placed in vacuum oven at 40°C for 16 hours.

Example 5

A combined solution/slurry of paroxetine hydrochloride hemihydrate (2%) and excipient (23%) in water was spray dried under the following conditions:

Apparatus:	Niro Mobile Minor
Feed Temperature:	62-70°C
Feed Rate:	1.30 kg/hr
Nozzle diameter	2.0 mm
Nozzle Air/Feed Ratio:	1.9
Inlet Temperature:	90°C
Outlet Temperature:	41-45°C
Drying Nitrogen Flow:	103 kg/hr
Duration:	24 minutes
Product wt:	84.5 g

Appearance:	Free moving white powder

The product was placed in vacuum oven at 40°C for 16 hours.

Example 6

A 5% solution of paroxetine hydrochloride hemihydrate in ethanol/water (96:4) was spray dried under the following conditions:

Apparatus:	Niro Mobile Minor
Feed Temperature:	29-32°C
Feed Rate:	2.3 kg/hr
Nozzle diameter	2.0 mm
Nozzle Air/Feed Ratio:	1.4
Inlet Temperature:	90°C
Outlet Temperature:	43-44°C
Drying Nitrogen Flow:	88 kg/hr
Duration:	26 minutes

Product wt:	36.8 g
Appearance:	Free moving white powder

The product was placed in vacuum oven at 40°C for 16 hours.

Example 7

A 5% solution of paroxetine hydrochloride hemihydrate in propan-2-ol/water (80:20) was spray dried under the following conditions:

Apparatus:	Niro Mobile Minor
Feed Temperature:	26-27°C
Feed Rate:	2.4 kg/hr
Nozzle diameter	2.0 mm
Nozzle Air/Feed Ratio:	2.1

Inlet Temperature:	90-110°C
Outlet Temperature:	42-47°C
Drying Nitrogen Flow:	89 kg/hr
Duration:	25 minutes

Product wt:	24.3 g
Appearance:	Free moving white powder

The product was placed in vacuum oven at 40°C for 16 hours.

Example 8

A 10% solution of paroxetine hydrochloride in propan-2-ol/water (80:20) was spray dried under the following conditions:

Apparatus:	Niro Mobile Minor
Feed Temperature:	26-28°C
Feed Rate:	2.7 kg/hr
Nozzle diameter	2.0 mm
Nozzle Air/Feed Ratio:	2.7
Inlet Temperature:	110°C
Outlet Temperature:	42-47°C
Drying Nitrogen Flow:	86 kg/hr
Duration:	22 minutes

Product wt:	27.5 g
Appearance:	Free moving white powder

The product was placed in vacuum oven at 40°C for 16 hours.

Example 9

A 20% solution of paroxetine hydrochloride hemihydrate in propan-2-ol/water (80:20) was spray dried under the following conditions:

Apparatus:	Niro Mobile Minor
Feed Temperature:	66-78°C
Feed Rate:	2.7 kg/hr
Nozzle diameter	2.0 mm
Nozzle Air/Feed Ratio:	2.6
Inlet Temperature:	90°C
Outlet Temperature:	46-48°C
Duration:	22 minutes
Drying Nitrogen Flow:	88 kg/hr

Product wt:	159.3 g
Appearance:	Free moving white powder

The product was placed in vacuum oven at 40°C for 16 hours.

Example 10

A 30% solution of paroxetine hydrochloride hemihydrate in propan-2-ol/water (50:50) was spray dried under the following conditions:

Apparatus:	Niro Mobile Minor
Feed Temperature:	42-65°C
Feed Rate:	0.9 kg/hr
Nozzle diameter	2.0 mm
Nozzle Air/Feed Ratio:	10.3
Inlet Temperature:	75°C
Outlet Temperature:	46-48°C
Drying Nitrogen Flow:	90 kg/hr
Duration:	34 minutes

Product wt:	110.0 g
Appearance:	Free moving white powder

The product was placed in vacuum oven at 40°C for 16 hours.

Example 11

A 30% solution of paroxetine hydrochloride hemihydrate in water was spray dried under the following conditions:

Apparatus:	Niro Mobile Minor
Feed Temperature:	80-90°C
Feed Rate:	0.7 kg/hr
Nozzle diameter	2.0 mm
Nozzle Air/Feed Ratio:	12.9
Inlet Temperature:	75°C
Outlet Temperature:	44°C
Drying Nitrogen Flow:	90 kg/hr
Duration:	43 minutes
Product wt:	123 g (81%)
Appearance:	Free moving white powder

The product was placed in vacuum oven at 40°C for 16 hours.

CLAIMS

1. A process for spray drying paroxetine hydrochloride from water-containing solutions, in which the outlet gas temperature is in the range 40-55°C, and the water content of the outlet gas is kept below 1.1 kg per 100 kg of outlet gas.

2. A process according to claim 1, in which the feedstock is a water-containing solution at a concentration of 5-50% by wt. paroxetine hydrochloride.

3. A process according to claim 2, in which the spray drying is carried out using water-containing solutions of paroxetine hydrochloride at concentrations of 10-25% by wt.

4. A process according to any preceding claim, in which the non-aqueous component of the solvent mixture is propan-2-ol, ethanol, or acetone.

5. A process for spray drying paroxetine hydrochloride in which the feedstock is an wholly aqueous solution containing 3-30% paroxetine hydrochloride at 60 to 95°C, the outlet gas temperature is in the range 40-55 °C, and the water content of the outlet gas is kept below 1.1 kg per 100 kg of outlet gas.

6. A process according to any preceding claim, in which the spray drying is carried out using pre-dried air.

7. A process according to any preceding claim, in which the spray drying is carried out using between 1 and 15 kg nozzle gas per kg feedstock

8. A process according to any preceding claim, in which the spray drying followed by post drying in an air or vacuum oven or a fluidised bed drier.

9. A process for spray drying paroxetine hydrochloride in which the feedstock is a water-containing solution or suspension of excipient(s) in the range 20-60% by wt. and paroxetine hydrochloride in the range 1-10% by wt., the outlet gas temperature is in the range 40-75 °C, and the water content of the outlet gas is kept below 1.1 kg per 100 kg of outlet gas.

10. A pharmaceutical composition for treatment or prophylaxis of the Disorders comprising paroxetine hydrochloride spray-dried according to any one of claims 1 to 9 and a pharmaceutically acceptable carrier, or an aqueous solution of reconstituted paroxetine hydrochloride spray-dried according to any one of claims 1 to 9.

11. Use of paroxetine hydrochloride spray-dried according to any one of claims 1 to 9 to manufacture a medicament in solid or reconstituted liquid form for the treatment or prophylaxis of the Disorders.

12. A method of treating the disorders which comprises administering an effective or prophylactic amount of paroxetine hydrochloride spray-dried according to any one of claims 1 to 9 as a solid oral composition or as a reconstituted aqueous oral or parenteral composition to a person suffering from one or more of the Disorders.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/20 — A2

(11) International Publication Number: **WO 99/58113**

(43) International Publication Date: 18 November 1999 (18.11.99)

(21) International Application Number: PCT/GB99/01520

(22) International Filing Date: 13 May 1999 (13.05.99)

(30) Priority Data:
9810181.9 13 May 1998 (13.05.98) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ELDER, David, Philip [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). LEONARD, Graham, Stanley [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: WEST, Vivien; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: NOVEL FORMULATION CONTAINING PAROXETINE

(57) Abstract

Paroxetine hydrochloride, in a form other than the hemihydrate, which is formulated into tablets under conditions such that there is no detectable conversion to hemihydrate during the tabletting process.

FOR THE PURPOSES OF INFORMATION ONLY

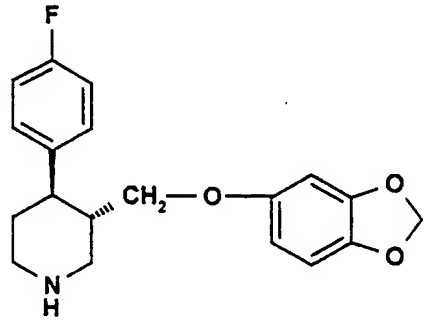
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

NOVEL FORMULATION CONTAINING PAROXETINE

The present invention relates to novel formulations and to the use of the formulations in the treatment and/or prevention of certain disorders.

US Patent 4,007,196 describes certain compounds which possess anti-depressant activity. One specific compound mentioned in this patent is known as paroxetine and has the following formula:



This compound has been approved for human use and is marketed, in the form of its hydrochloride salt, in many countries around the world as an anti-depressant agent.

All paroxetine hydrochloride sold to date has been in the form of oral swallow tablets, containing the hemihydrate, which is described in EP-0 223 403. Paroxetine hydrochloride has been reported as also existing as an anhydrate. WO 96/24595 describes the preparation and physical properties of four different polymorphic forms (Forms A, B, C and D) of the anhydrate.

WO 95/16448 discloses that paroxetine is likely to develop a pink colour unless it is formulated into tablets using a formulation process in which water is absent, such as dry direct compression of paroxetine or dry granulation of paroxetine followed by compression into tablets. The term "dry" was used to denote substantially dry as opposed to the wholesale addition of water which had been previously employed in the wet granulation process.

It has now surprisingly been found that, even under these relatively dry conditions, paroxetine hydrochloride anhydrate has a tendency to convert at least partially to the hemihydrate during the tabletting process. Although not dangerous, this creates difficulties in establishing and maintaining a reference standard for regulatory and quality control purposes.

Accordingly, the present invention provides paroxetine hydrochloride, in a form other than the hemihydrate, which is formulated into tablets under conditions such there is no detectable conversion to hemihydrate during the tabletting process.

The paroxetine hydrochloride may, for example be amorphous or in the form of a crystalline anhydrate.

This can be achieved for example by the use of excipients which are essentially anhydrous. That is to say, they contain less than 2%, more especially less than 1.5%, preferably less than 1% water.

It has been found for example that dibasic calcium phosphate anhydrous can be used to form oral swallow tablets with paroxetine hydrochloride anhydrate without undesired conversion to hemihydrate during the tabletting process.

The tabletting process may for example comprise dry direct compression of paroxetine or dry granulation of paroxetine followed by compression into tablets. Preferably, the tablets are then packaged with a desiccant in order to prevent conversion of anhydrate to hemihydrate on storage.

Accordingly, the present invention also provides a process for the preparation of paroxetine hydrochloride anhydrate tablets free of detectable hemihydrate which is characterised by the use of conditions such there is no detectable conversion of the anhydrate to hemihydrate during the tabletting process. Such conditions can be achieved by the use of essentially anhydrous excipients. Advantageously, tabletting can also be carried out under conditions of low relative humidity

Examples of excipients with the necessary low moisture content suitable for direct compression include materials such as dibasic calcium phosphate anhydrous, anhydrous direct compression lactose, monosaccharide sugars eg mannitol, disaccharide sugars eg lactitol, powdered cellulose, pregelatinised starch and similar materials. Dibasic calcium phosphate anhydrous is commercially available in a pharmaceutically acceptable grade, eg A-TAB (Rhone Poulenc). Anhydrous direct compression lactose is commercially available in a pharmaceutically acceptable grade, eg anhydrous direct tabletting (Quest International Inc). Additionally, certain of the low moisture sugars available in direct compression grades eg mannitol and lactitol can improve the palatibility of the formulation by masking the bitter taste of paroxetine. Direct compression lactilol is commercially available in a pharmaceutically acceptable grade, eg Finlac DC (Xyrofin).

In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with dibasic calcium phosphate anhydrous, and/or anhydrous direct compression grade lactose(s), and/or microcrystalline cellulose (in particular A-TAB, lactose anhydrous direct tabletting, and Avicel PH112 dried to a moisture content of 0.8-1.5%) in a suitable blender. Other pharmaceutically acceptable excipients may also be added such as disintegrants eg sodium starch glycolate, croscarmellose sodium, and colloidal silicon dioxide (in particular Explotab (dried to a moisture content of < 2%), Ac-Di-Sol, and Syloid 244, respectively): lubricants such as magnesium stearate: and glidants such as colloidal silicon dioxide, and talc.

The composition is then mixed and compressed using standard pharmaceutical procedures. As an additional aid to the protection of this product from the deleterious affects of moisture the tablets can be film coated. Standard aqueous film coating is not appropiate for such a moisture sensitive product; however, the tablets can be coated with hydrophobic coating materials, such as glyceryl behenate, using a hot melt coating technique. In a particular process of the invention, tablet cores are coated with a 2% w/w of glyceryl behenate (in particular Compritol 888). 2% levels of glyceryl behenate do not adversely affect the dissolution of the dosage form in the gastric environment. Glyceryl behenate is commercially available in a pharmaceutically acceptable grade, eg Compritol 888 (Gattefosse). A modified aqueous film coating procedure using Opadry AMB (Aqueous Moisture Barrier) can also be utilised. In a particular process of the invention, tablet cores are coated with a 2% w/w of Opadry AMB. Opadry AMB is commercially available in a pharmaceutically acceptable grade, eg Opadry OY-B-31006 (Colorcon).

Coated tablets are then packaged in standard pharmaceutical container/closure presentations, optionally with a desiccant.

Typical compositional ranges of key excipients on a w/w basis are provided : Preferably the amounts of lubricants are in the range 0.5 to 2.0%, most preferably 0.5 to 1.0%. The disintegrants are controlled in the range 0.5 to 8.0%, most preferably 2.0 to 4.0%. Preferably the amounts of anhydrous diluents are controlled in the range 50.0 to 95.0%. Mixtures of the principal diluents can be used to assist in flow and compression properties of the formulation. Preferably the amounts of film coat are controlled in the range 1.0 to 3.0%, most preferably 2.0%.

The amount of paroxetine used is adjusted such that in a single unit dose there is a therapeutically effective amount of paroxetine. Preferably the unit dose contains from

10 to 100 mg paroxetine (as measured in terms of the free base). More preferable the amount of paroxetine in a unit dose is 10mg, 20mg, 30mg, 40mg or 50mg. The most preferred amount of paroxetine in a unit dose is 20mg.
Paroxetine used in the formulation is in the form of the hydrochloride anhydrate which may be prepared according to the procedures outlined in WO 96/24595. Suitable procedures for preparing paroxetine include those mentioned in US Patents 4.009.196, 4.902.801, 4.861.893 and 5,039.803 and PCT/GB 93/00721.

It has been mentioned that paroxetine has particular utility in the treatment of depression; paroxetine may also be used in the treatment of mixed anxiety and depression. obsessive compulsive disorders, panic, pain, obesity, senile dementia, migraine. bulimia. anorexia, social phobia and the depression arising from pre-menstrual tension and adolescence.

The present invention therefore also provides a method of treating or preventing any of the above disorders which comprises administering an effective or prophylactic amount of an oral swallow tablet prepared in accordance with the present invention.

The following examples illustrate the present invention:

Example 1

	mg
Paroxetine hydrochloride †	22.22
Dibasic Calcium Phosphate Anhydrous	220.28
Sodium Starch Glycolate	5.00
Magnesium Stearate	2.50
Tablet weight	250.00

Example 2

	mg
Paroxetine hydrochloride †	22.22
Dibasic Calcium Phosphate Anhydrous	171.78
Sodium Starch Glycolate	4.00
Magnesium Stearate	2.00
Tablet weight	200.00

Example 3

	mg
Paroxetine hydrochloride †	22.22
Dibasic Calcium Phosphate Anhydrous	123.28
Sodium Starch Glycolate	3.00
Magnesium Stearate	1.50
Tablet weight	150.00

Example 4

	mg
Paroxetine hydrochloride †	22.22
Dibasic Calcium Phosphate Anhydrous	224.03
Croscarmellose Sodium	1.25
Magnesium Stearate	2.50
Tablet weight	250.00

Example 5

	mg
Paroxetine hydrochloride †	22.22
Dibasic Calcium Phosphate Anhydrous	225.28
Magnesium Stearate	2.50
Tablet weight	250.00

Example 6

	mg
Paroxetine hydrochloride †	22.22
Dibasic Calcium Phosphate Anhydrous	224.03
Colloidal Silicone Dioxide	1.25
Magnesium Stearate	2.50
Tablet weight	250.00

Example 7

	mg
Paroxetine hydrochloride †	22.22
Dibasic Calcium Phosphate Anhydrous	125.00
Microcrystalline Cellulose	95.28
Sodium Starch Glycolate	5.00
Magnesium Stearate	2.50
Tablet weight	250.00

Example 8

	mg
Paroxetine hydrochloride †	22.22
Dibasic Calcium Phosphate Anhydrous	125.00
Lactose Anhydrous	95.28
Sodium Starch Glycolate	5.00
Magnesium Stearate	2.50
Tablet weight	250.00

Example 9

	mg
Paroxetine hydrochloride †	22.22
Lactose Anhydrous	220.28
Sodium Starch Glycolate	5.00
Magnesium Stearate	2.50
Tablet weight	250.00

Example 10

	mg
Paroxetine hydrochloride †	22.22
Lactose Anhydrous	171.78
Sodium Starch Glycolate	4.00
Magnesium Stearate	2.00
Tablet weight	200.00

Example 11

	mg
Paroxetine hydrochloride †	22.22
Lactose Anhydrous	123.28
Sodium Starch Glycolate	3.00
Magnesium Stearate	1.50
Tablet weight	150.00

Example 12

	mg
Paroxetine hydrochloride †	22.22
Direct compression Lactitol	220.28
Sodium Starch Glycolate	5.00
Magnesium Stearate	2.50
Tablet weight	250.00

Example 13

	mg
Paroxetine hydrochloride †	22.22
Lactose Anhydrous	220.28
Sodium Starch Glycolate	5.00
Magnesium Stearate	2.50
Compritol 888	2.50
Tablet weight	252.50

Example 14

	mg
Paroxetine hydrochloride †	22.22
Lactose Anhydrous	171.78
Sodium Starch Glycolate	4.00
Magnesium Stearate	2.00
Compritol 888	2.0
Tablet weight	202.00

Example 15

	mg
Paroxetine hydrochloride †	22.22
Lactose Anhydrous	123.28
Sodium Starch Glycolate	3.00
Magnesium Stearate	1.50
Compritol 888	1.50
Tablet weight	151.50

Example 16

	mg
Paroxetine hydrochloride †	22.22
Lactose Anhydrous	220.28
Sodium Starch Glycolate	5.00
Magnesium Stearate	2.50
Opadry AMB	2.50
Tablet weight	252.50

Example 17

	mg
Paroxetine hydrochloride †	22.22
Lactose Anhydrous	171.78
Sodium Starch Glycolate	4.00
Magnesium Stearate	2.00
Opadry AMB	2.0
Tablet weight	202.00

Example 18

	mg
Paroxetine hydrochloride †	22.22
Lactose Anhydrous	123.28
Sodium Starch Glycolate	3.00
Magnesium Stearate	1.50
Opadry AMB	1.5
Tablet weight	151.50

† Equivalent to 20 mg of Paroxetine on an anhydrous free base basis

Claims

1. Paroxetine hydrochloride, in a form other than the hemihydrate, which is formulated into tablets under conditions such there is no detectable conversion to hemihydrate during the tabletting process.

2. Paroxetine hydrochloride according to claim 1 which is amorphous or in the form of a crystalline anhydrate.

3. A process for the preparation of paroxetine hydrochloride tablets free of detectable hemihydrate which is characterised by the use of conditions such there is no detectable conversion to hemihydrate during the tabletting process.

4. A process according to claim 3 which comprises dry direct compression of paroxetine or dry granulation of paroxetine followed by compression into tablets.

5. A process according to claim 3 or 4 which is carried out using essentially anhydrous excipients.

6. A process according to claim 5 wherein the excipients are chosen from the group consisting of dibasic calcium phosphate anhydrous, anhydrous direct compression lactose, monosaccharide sugars, disaccharide sugars, powdered cellulose, and pregelatinised starch.

7. A process according to any one of claims 3 to 6 which is carried out under conditions of low relative humidity.

8. A process according to any one of claims 3 to 7, further comprising the application of a non-aqueous film coating.

9. A kit of parts comprising tablets according to claim 1or 2 or obtainable by the process of any one of claims 3 to 8, together with a desiccant.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/20, 31/445

A3

(11) International Publication Number: **WO 99/58113**

(43) International Publication Date: 18 November 1999 (18.11.99)

(21) International Application Number: PCT/GB99/01520

(22) International Filing Date: 13 May 1999 (13.05.99)

(30) Priority Data:
9810181.9 13 May 1998 (13.05.98) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ELDER, David, Philip [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). LEONARD, Graham, Stanley [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: WEST, Vivien; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
17 February 2000 (17.02.00)

(54) Title: NOVEL FORMULATION CONTAINING PAROXETINE

(57) Abstract

Paroxetine hydrochloride, in a form other than the hemihydrate, which is formulated into tablets under conditions such that there is no detectable conversion to hemihydrate during the tabletting process.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

Inter ınal Application No
PCT/GB 99/01520

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 09963 A (PENTECH) 12 March 1998 (1998-03-12) claims examples	1-3
A	WO 95 16448 A (SMITHKLINE BEECHAM) 22 June 1995 (1995-06-22) cited in the application claims examples	1-9
X,P	WO 98 31365 A (SMITHKLINE BEECHAM) 23 July 1998 (1998-07-23) claims 1,3,5,6,8	1-3

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 December 1999	21/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

1

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/GB 99/01520

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
E	WO 99 32092 A (SMITHKLINE BEECHAM) 1 July 1999 (1999-07-01) claims 1,4,13,14 examples 2,8	1,3-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/GB 99/01520

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9809963 A	12-03-1998	US 5672612 A	30-09-1997
		EP 0931080 A	28-07-1999
		GB 2331519 A	26-05-1999
WO 9516448 A	22-06-1995	AP 540 A	20-09-1996
		AT 180973 T	15-06-1999
		AU 697982 B	22-10-1998
		AU 1314595 A	03-07-1995
		BG 100648 A	28-02-1997
		BR 9408219 A	26-08-1997
		CA 2178637 A,C	22-06-1995
		CA 2214575 A	22-06-1995
		CN 1137236 A	04-12-1996
		CZ 9601763 A	11-09-1996
		DE 69419033 D	15-07-1999
		DE 69419033 T	25-11-1999
		EP 0734260 A	02-10-1996
		ES 2132610 T	16-08-1999
		FI 962445 A	12-06-1996
		HU 75880 A	28-05-1997
		JP 9506602 T	30-06-1997
		NO 962547 A	14-06-1996
		NZ 277790 A	26-02-1998
		PL 314980 A	30-09-1996
		SI 734260 T	31-08-1999
		SK 75696 A	06-11-1996
		ZA 9409900 A	10-10-1995
WO 9831365 A	23-07-1998	AU 5567398 A	07-08-1998
		EP 0952831 A	03-11-1999
		NO 993460 A	14-09-1999
WO 9932092 A	01-07-1999	AU 1931999 A	12-07-1999

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/48 — A2

(11) International Publication Number: **WO 99/58116**

(43) International Publication Date: 18 November 1999 (18.11.99)

(21) International Application Number: PCT/GB99/01522

(22) International Filing Date: 13 May 1999 (13.05.99)

(30) Priority Data:
9810180.1 13 May 1998 (13.05.98) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ELDER, David, Philip [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). LEONARD, Graham, Stanley [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: WEST, Vivien; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: NOVEL FORMULATION CONTAINING PAROXETINE

(57) Abstract

Paroxetine hydrochloride, in a form other than the hemihydrate, which is formulated into capsules under conditions such there is no detectable conversion to hemihydrate during the manufacturing process.

FOR THE PURPOSES OF INFORMATION ONLY

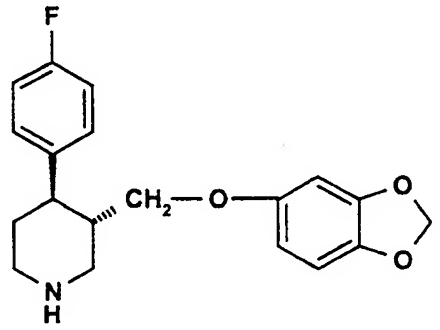
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

NOVEL FORMULATION CONTAINING PAROXETINE

The present invention relates to novel formulations and to the use of the formulations in the treatment and/or prevention of certain disorders.

US Patent 4,007,196 describes certain compounds which possess anti-depressant activity. One specific compound mentioned in this patent is known as paroxetine and has the following formula:



This compound has been approved for human use and is marketed, in the form of its hydrochloride salt, in many countries around the world as an anti-depressant agent.

All paroxetine hydrochloride sold to date has been in the form of oral swallow tablets, containing the hemihydrate, which is described in EP-0 223 403. Paroxetine hydrochloride has been reported as also existing as an anhydrate. WO 96/24595 describes the preparation and physical properties of four different polymorphic forms (Forms A, B, C and D) of the anhydrate.

WO 95/16448 discloses that paroxetine is likely to develop a pink colour unless it is formulated into tablets using a formulation process in which water is absent, such as dry direct compression of paroxetine or dry granulation of paroxetine followed by compression into tablets. The term "dry" was used to denote substantially dry as opposed to the wholesale addition of water which had been previously employed in the wet granulation process.

It has now surprisingly been found that, even under these relatively dry conditions, paroxetine hydrochloride anhydrate has a tendency to convert at least partially to the hemihydrate during the tabletting process. Although not dangerous, this creates difficulties in establishing and maintaining a reference standard for regulatory and quality control purposes.

Accordingly, the present invention provides paroxetine hydrochloride in a form other than the hemihydrate, which is formulated into capsules under conditions such there is no detectable conversion to hemihydrate during the manufacturing process.

The paroxetine hydrochloride may, for example, be present in an amorphous form or as a crystalline anhydrate.

This can be achieved for example by the use of either excipients which are essentially anhydrous for powder fill capsules (that is to say, they contain less than 2%, more especially less than 1.5%, preferably less than 1% water) or excipients which are essentially hydrophobic for solid or liquid filled capsules.

It has been found for example that dibasic calcium phosphate anhydrous and polyglycolized glycerides can be used to form oral swallow capsules with paroxetine hydrochloride anhydrate without undesired conversion to hemihydrate during the manufacturing process. The capsules are then packaged with a desiccant in order to prevent conversion of anhydrate to hemihydrate on storage.

Accordingly, the present invention also provides a process for the preparation of paroxetine hydrochloride anhydrate capsules free of detectable hemihydrate which is characterised by the use of conditions such there is no detectable conversion of the anhydrate to hemihydrate during the manufacturing process. Such conditions can be achieved by the use of essentially anhydrous/hydrophobic excipients under conditions of low relative humidity

Examples of excipients with the necessary low moisture content include materials such as dibasic calcium phosphate anhydrous, anhydrous direct compression lactose, monosaccharide sugars eg mannitol, disaccharide sugars eg lactitol, powdered cellulose, pregelatinised starch and similar materials. These materials may also be of a grade suitable for direct compression, as this can aid powder filling on the capsule filling machine and also impart appropriate compression characteristics on the blend as appropriate for certain types of capsule filling machines. Dibasic calcium phosphate anhydrous is commercially available in a pharmaceutically acceptable grade, eg A-TAB (Rhone Poulenc) as the main excipient in a powder fill capsules formulation. In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with dibasic calcium phosphate anhydrous and other pharmaceutically acceptable excipients such as a lubricant eg magnesium stearate and mixed in a suitable blender before filling cellulose capsule shells of intrinsically low moisture content (eg Shionogi Qualicaps, < 3%). Additionally, certain of the low

moisture sugars are available in direct compression grades eg mannitol and lactitol; direct compression lactilol is commercially available in a pharmaceutically acceptable grade, eg Finlac DC (Xyrofin). In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with direct compression lactilol and other pharmaceutically acceptable excipients such as a lubricant eg magnesium stearate and mixed in a suitable blender before filling cellulose capsule shells of intrinsically low moisture content (eg Shionogi Qualicaps, < 3%).

Examples of excipients with the necessary hydrophobicity include materials such as polyglycolised glycerides eg Gelucire 44/14; complex fatty materials of plant origin eg theobroma oil, carnauba wax; plant oils eg peanut, olive, palm kernels, cotton, corn, soya; hydrogenated plant oils eg peanut, palm kernels, cotton, soya, castor, coconut; natural fatty materials of animal origin eg beeswax, lanolin, fatty alcohols eg cetyl, stearyl, lauric, myristic, palmitic, stearic; esters eg glycerol stearate, glycol stearate, ethyl oleate, isopropyl myristate; solid interesterified semi-synthetic glycerides eg suppocire, witepsol; liquid interesterified semi-synthetic glycerides eg miglyol 810/812, labrafil; amide or fatty acid alcolamides eg stearamide ethanol, diethanolamide of fatty coconut acids; polyoxyethylene glycols eg PEG 400, PEG 600, PEG 4000.

An appropriate plant oil eg peanut oil (arachis oil) is commercially available in a pharmaceutically acceptable grade eg Lipex 101 (Karlshamns). In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with warm Lipex 101 in a suitable blender (to form a suspension) before filling into gelatin capsule shells.

A hydrogenated plant oil is commercially available in a pharmaceutically acceptable grade eg Lubritab (Edward Mendell). In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with molten Lubritab in a suitable blender, a hydrophilic excipent, for example anhydrous lactose is added (to form a suspension) before filling into gelatin capsule shells.

An appropriate fatty alcohol eg cetyl alcohol is commercially available in a pharmaceutically acceptable grade eg Crodacol C95 (Croda). In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with molten Crodacol C95 in a suitable blender (to form a suspension) before filling into gelatin capsule shells.

A polyglycolised glyceride is commercially available in a pharmaceutically acceptable grade eg Gelucire 44/14 (Gattfosse). In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with molten Gelucire 44/14 in a suitable blender (to form a solid suspension) before filling gelatin capsule shells.

A liquid interesterified semi-synthetic glycerides is commercially available in a pharmaceutically acceptable grade eg Labrafil M 2125CS (Gattfosse) or Miglyol 810/812 (Hull). In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with Labrafil M 2125CS (Gatfosse) to produce a suspension in a hard or soft gelatin capsule formulation. Alternatively, paroxetine hydrochloride anhydrate is mixed with Miglyol 810 (H©ls AG) in a suitable mixer to produce a suspension in a hard or soft gelatin capsule formulation.

A solid interesterified semi-synthetic glycerides is commercially available in a pharmaceutically acceptable grade eg Suppocire AM - DM (Gattfosse). In a particular process of the invention, (example 4) paroxetine hydrochloride anhydrate is mixed with molten Suppocire DM in a suitable blender (to form a suspension) before filling into gelatin capsule shells.

The capsule formulation is packaged in standard pharmaceutical container/closure presentations, optionally with a desiccant.

The amount of paroxetine used is adjusted such that in a single unit dose there is a therapeutically effective amount of paroxetine. Preferably the unit dose contains from 10 to 100 mg paroxetine (as measured in terms of the free base). More preferable the amount of paroxetine in a unit dose is 10mg, 20mg, 30mg, 40mg or 50mg. The most preferred amount of paroxetine in a unit dose is 20mg.
Paroxetine used in the formulation is in the form of the hydrochloride anhydrate which may be prepared according to the procedures outlined in WO 96/24595. Suitable procedures for preparing paroxetine include those mentioned in US Patents 4,009,196, 4,902,801, 4,861,893 and 5,039,803 and PCT/GB 93/00721.

It has been mentioned that paroxetine has particular utility in the treatment of depression; paroxetine may also be used in the treatment of mixed anxiety and depression, obsessive compulsive disorders, panic, pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia and the depression arising from pre-menstrual tension and adolescence.

The present invention therefore also provides a method of treating or preventing any of the above disorders which comprises administering an effective or prophylactic amount of an oral swallow capsule prepared in accordance with the present invention.

The following examples illustrate the present invention:

Example 1

	mg
Paroxetine hydrochloride †	22.22
Dibasic Calcium Phosphate Anhydrous	225.28
Magnesium Stearate	2.50
Capsule weight	250.00

Example 2

	mg
Paroxetine hydrochloride †	22.22
Direct compression Lactitol	225.28
Magnesium Stearate	2.50
Capsule weight	250.00

Example 3

	mg
Paroxetine hydrochloride †	22.22
Lactose Anhydrous	225.28
Magnesium Stearate	2.50
Capsule weight	250.00

Example 4

	mg
Paroxetine hydrochloride †	22.22
Lactose Anhydrous	175.78
Magnesium Stearate	2.00
Capsule weight	200.00

Example 5

	mg
Paroxetine hydrochloride †	22.22
Lactose Anhydrous	126.28
Magnesium Stearate	1.50
Capsule weight	150.00

Example 6

	mg
Paroxetine hydrochloride †	22.22
Lipex 101	227.78
Capsule weight	250.00

Example 7

	mg
Paroxetine hydrochloride †	22.22
Anhydrous Lactose	50.0
Lubritab	177.78
Capsule weight	250.00

Example 8

	mg
Paroxetine hydrochloride †	22.22
Crodacol C95	227.78
Capsule weight	250.00

Example 9

	mg
Paroxetine hydrochloride †	22.22
Gelucire 44/14	227.78
Capsule weight	250.00

Example 10

	mg
Paroxetine hydrochloride †	22.22
Labrafil M 2125CS	227.78
Capsule weight	250.00

Example 11

	mg
Paroxetine hydrochloride †	22.22
Miglyol 810	227.78
Capsule weight	250.00

Example 12

	mg
Paroxetine hydrochloride †	22.22
Suppocire DM	227.78
Capsule weight	250.00

† Equivalent to 20 mg of Paroxetine on an anhydrous free base basis

Claims

1. Paroxetine hydrochloride, in a form other than the hemihydrate, which is formulated into capsules under conditions such there is no detectable conversion to hemihydrate during the manufacturing process.

2. Paroxetine hydrochloride according to claim 1 which is amorphous or in the form of a crystalline anhydrate.

3. A process for the preparation of paroxetine hydrochloride capsules free of detectable hemihydrate which is characterised by the use of conditions such there is no detectable conversion to hemihydrate during the tabletting process.

4. A process according to claim 3 which is carried out using essentially anhydrous and/or hydrophobic excipients.

5. A process according to claim 4 wherein the excipients are chosen from the group consisting of dibasic calcium phosphate anhydrous, anhydrous direct compression lactose, monosaccharide sugars, disaccharide sugars, powdered cellulose, and pregelatinised starch.

6. A process according to claim 4 wherein the excipients are chosen from the group consisting of polyglycolised glycerides; complex fatty materials of plant origin, plant oils, hydrogenated plant oils, natural fatty materials of animal origin, fatty alcohols; esters; solid interesterified semi-synthetic glycerides; liquid interesterified semi-synthetic glycerides; amide or fatty acid alcolamides; and polyoxyethylene glycols.

7. A process according to any one of claims 3 to 6 which is carried out under conditions of low relative humidity.

8. A kit of parts comprising capsules according to claim 1or 2 or obtainable by the process of any one of claims 3 to 7, together with a desiccant.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/48, 31/445 — A3

(11) International Publication Number: **WO 99/58116**

(43) International Publication Date: 18 November 1999 (18.11.99)

(21) International Application Number: PCT/GB99/01522

(22) International Filing Date: 13 May 1999 (13.05.99)

(30) Priority Data:
9810180.1 13 May 1998 (13.05.98) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ELDER, David, Philip [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). LEONARD, Graham, Stanley [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: WEST, Vivien; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
17 February 2000 (17.02.00)

(54) Title: NOVEL FORMULATION CONTAINING PAROXETINE

(57) Abstract

Paroxetine hydrochloride, in a form other than the hemihydrate, which is formulated into capsules under conditions such there is no detectable conversion to hemihydrate during the manufacturing process.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

nter onal Application No
PCT/GB 99/01522

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/48 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 99 26625 A (SMITHKLINE BEECHAM) 3 June 1999 (1999-06-03) claims 1,2,4,5,10-14,17,18 page 2, line 32 -page 3, line 7 page 6, line 31 - line 36	1-8
A	WO 96 31197 A (ABBOTT) 10 October 1996 (1996-10-10) claims 1,2,5-7,11,12,15	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

' Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 December 1999	22/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

Form PCT ISA 210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter... nal Application No
PCT/GB 99/01522

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9926625 A	03-06-1999	AU 1168099 A	15-06-1999
WO 9631197 A	10-10-1996	CA 2216934 A	10-10-1996
		EP 0818990 A	21-01-1998
		JP 11503163 T	23-03-1999
		US 5807574 A	15-09-1998

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/445, 9/14, 9/16 — A1

(11) International Publication Number: **WO 98/31365**

(43) International Publication Date: 23 July 1998 (23.07.98)

(21) International Application Number: PCT/GB98/00081

(22) International Filing Date: 12 January 1998 (12.01.98)

(30) Priority Data:

9700692.8	15 January 1997 (15.01.97)	GB
9714873.8	15 July 1997 (15.07.97)	GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: JACEWICZ, Victor, Witold [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). WARD, Neal [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB).

(74) Agent: GIDDINGS, Peter, John; SmithKline Beecham plc, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PAROXETINE COMPOSITIONS

(57) Abstract

Paroxetine hydrochloride is obtained in a free-flowing and easily soluble form (suitable for preparing solid formulations or aqueous solutions, suitable for parenteral use) by spray-drying solutions of paroxetine hydrochloride hemihydrate or other anhydrate/hydrate/solvate/amorphous forms.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

PAROXETINE COMPOSITIONS

The present invention relates to a process for the preparation of a pharmaceutically active compound, and to use of the so-prepared compound in therapy. In particular this invention is concerned with the preparation of a free-flowing form of paroxetine hydrochloride.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US-A-3912743 and US-A-4007196. An especially important compound among those disclosed is paroxetine, the (-)*trans* isomer of 4-(4'-fluorophenyl)-3',4'-methylenedioxy-phenoxymethyl)-piperidine. This compound is used in therapy as the hydrochloride salt to treat *inter alia* depression, obsessive compulsive disorder (OCD) and panic.

Paroxetine hydrochloride has been described in the literature as a crystalline hemihydrate (see EP-A-0223403 of Beecham Group) and as various crystalline anhydrate forms (see WO96/24595 of SmithKline Beecham plc). These known forms have properties that are not ideal for all pharmaceutical applications, and are prepared by multi-step procedures involving precipitation under carefully controlled conditions, filtration, drying, and homogenisation. The preferred crystallisation procedures utilise organic solvents which, when compared to water, are costly and are associated with safety and environmental problems. Furthermore, the difficulty of producing crystalline products with a uniform and regular particle size causes problems with formulation by encapsulation. Also, the flow characteristics of crystalline products limit the choice of bulk transfer and formulation technologies that can be used, while dust formation and electrostatic properties can be hazardous. In addition, the known sold forms of paroxetine hydrochloride are relatively insoluble and are slow to dissolve completely.

There remains a need for a form of paroxetine hydrochloride with improved processing and formulation characteristics.

According to a first aspect of the invention, there is provided a process for preparing a free-flowing form of paroxetine hydrochloride which comprises spray drying a solution of paroxetine hydrochloride.

The feedstock for spray drying may be prepared conveniently by, for example, dissolution of paroxetine free base in aqueous hydrochloric acid, although other solid forms of paroxetine hydrochloride may also be dissolved. For example, the feedstock may be prepared by dissolving amorphous paroxetine hydrochloride or a crystalline paroxetine hydrochloride anhydrate, hydrate or solvate in suitable solvent. The solvent used may be

pure water or a mixture of water with compatible organic solvents. Suitable compatible organic solvents include pyridinem acetic acid, acetonitrile, acetone, ethanol, propan-1-ol, butan-1-ol and tetrahydrofuran. Or alternatively a suitable organic solvent may be used on its own to form a solution with paroxetine hydrochloride. Some heating may be used to achieve and maintain complete solution, though once dissolved and in the absence of seeds of a crystalline form, aqueous solutions are stable at ambient temperature for many days. Suitable concentrations of paroxetine hydrochloride for spray-drying are in the range 1 to 30% by weight, preferably in the range 5% to 20% by weight.

Using conventional spray-drying procedures under normal conditions, often results in paroxetine hydrochloride particles that are sticky and adhere to the sides of the apparatus and to each other. However, when apparatus and operating conditions are selected to ensure that the particles are cooled sufficiently before they strike the apparatus walls, successful spray-drying may be carried out. Careful control of drop size in the spray nozzles, air flow rates and temperatures is needed to suit the apparatus used.

The paroxetine product of the above process is free-flowing, is readily wetted, and dissolves rapidly; solutions with high concentrations may be prepared without recourse to heating.

Accordingly, a second aspect of this invention is spray-dried paroxetine hydrochloride.

Spray-dried paroxetine hydrochloride of this invention has been found to be particularly suitable for applications where uniform particle size and good flow properties are advantageous. Furthermore as a result of the close control of particle size possible by spray-drying, the product may be handled conveniently and safely without the hazards associated with the dust produced when conventionally prepared paroxetine hydrochloride solids are prepared. Examples of applications where uniform particle size are advantageous include controlled release and microencapsulation (coated particle technology). Samples may be produced with particle sizes for specific applications, for example in the range 10-1000 microns.

Microencapsulation may be incorporated into the spray-drying process or may be carried out in a subsequent step. This technology is useful for taste masking, rapid or controlled release formulations, hence control of pharmacokinetics including the matching of pharmacokinetic properties for combination products.

Isolation of the solid product from the feedstock solution may be possible with just one processing stage; and so there is generally no need for blending, granulating, or drying, though an extra drying stage may be added if required. Providing aqueous feedstocks are used the costs and environmental problems normally associated with organic solvents are entirely avoided.

The spray-dried product of this invention may be formulated for therapy in the dosage forms described in EP-A-0223403 or WO96/24595. The free-flowing properties are advantageous for the preparation of solid formulations. Also the easily soluble nature of spray dried paroxetine hydrochloride makes it suitable for the preparation of solutions for parenteral use.

Therapeutic uses of the paroxetine product of this invention include treatment of: alcoholism, anxiety, depression, obsessive compulsive disorder, panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, pre-menstrual syndrome (PMS), adolescent depression, trichotillomania, dysthymia, and substance abuse, referred to below as "the disorders".

Accordingly, the present invention also provides:

a pharmaceutical composition for treatment or prophylaxis of the disorders comprising spray-dried paroxetine hydrochloride and a pharmaceutically acceptable carrier or an aqueous solution of reconstituted spray-dried paroxetine hydrochloride;

the use of spray-dried paroxetine hydrochloride to manufacture a medicament in solid or reconstituted liquid form for the treatment or prophylaxis of the disorders; and

a method of treating the disorders which comprises administering an effective or prophylactic amount of spray-dried paroxetine hydrochloride as a solid oral composition or as a reconstituted aqueous oral or parenteral composition to a person suffering from one or more of the disorders.

The invention is illustrated by the following Example..

Example:

A 10% aqueous solution of paroxetine hydrochloride is spray-dried under the following conditions:

Apparatus:	Niro Fielder Mobile Minor
Inlet temperature setting:	185°C
Actual inlet temperature:	184-185°C
Outlet temperature:	94-95°C
Atomiser speed:	40,000 - 50,000 rpm
Pump speed (peristaltic):	32-34 rpm
Air supply	4.8 - 5.2 bar
DP across filters:	
Bag filter:	start of run 57 mm of water
	end of run 65 mm of water
Hepa filter:	start of run 7 mm of water
	end of run 7 mm of water
DP across the orifice plate:	start of run 80+ mm of water
	end of run 80+ mm of water

CLAIMS

1. A process for preparing a free-flowing form of paroxetine hydrochloride which comprises spray drying a solution of paroxetine hydrochloride.

2. A process according to claim 1, in which the feedstock for spray drying is prepared by dissolution of paroxetine free base in aqueous hydrochloric acid.

3. A process according to claim 1, in which the feedstock is prepared by dissolving amorphous paroxetine hydrochloride or a crystalline paroxetine hydrochloride anhydrate, hydrate or solvate in a suitable solvent.

4. A process according to claim 1,2 or 3, in which the solvent is pure water or a mixture of water with one or more compatible organic solvents.

5. A process according to claim 1 or 3 in which the solution of paroxetine hydrochloride is in a suitable organic solvent in the absence of water.

6. A process according to claim 4 or 5 in which the organic solvent is selected from pyridine, acetic acid, acetonitrile, acetone, ethanol, propan-1-ol, butan-1-ol, or tetrahydrofuran

7. A process according to any one of the preceding claims, wherein the concentration of paroxetine hydrochloride is in the range 5% to 20% by weight.

8. Spray-dried paroxetine hydrochloride.

9. A pharmaceutical composition for treatment or prophylaxis of the disorders comprising spray-dried paroxetine hydrochloride and a pharmaceutically acceptable carrier or an aqueous solution of reconstituted spray-dried paroxetine hydrochloride.

10. The use of spray-dried paroxetine hydrochloride to manufacture a medicament in solid or reconstituted liquid form for the treatment or prophylaxis of the disorders.

11. A method of treating the disorders which comprises administering an effective or prophylactic amount of spray-dried paroxetine hydrochloride as a solid oral composition or as a reconstituted aqueous oral or parenteral composition to a person suffering from one or more of the disorders.

12. A composition according to claim 9, use according to claim 10, or a method according to claim 11, wherein the spray-dried paroxetine hydrochloride is the product of a process claimed in any one of claims 1 to 7.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 98/00081

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/445 A61K9/14 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	EP 0 810 224 A (ASAHI) 3 December 1997 see claims see examples ---	1,2,5,6, 8
A	GB 2 297 550 A (SMITHKLINE BEECHAM) 7 August 1996 cited in the application see the whole document -----	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 May 1998	27.05.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Interr nal Application No
PCT/GB 98/00081

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 810224 A	03-12-1997	CA 2206592 A	30-11-1997
		JP 10045756 A	17-02-1998
GB 2297550 A	07-08-1996	CY 2015 A	20-02-1998
		AU 4332896 A	15-08-1996
		AU 4786496 A	27-08-1996
		BE 1009112 A	05-11-1996
		BG 100333 A	30-08-1996
		BR 9600534 A	13-05-1997
		CA 2168829 A,C	07-08-1996
		CA 2210022 A	07-08-1996
		CA 2211521 A	07-08-1996
		CA 2211522 A	07-08-1996
		CH 688353 A	15-08-1997
		CN 1143643 A	26-02-1997
		CZ 9600320 A	14-08-1996
		DE 19603797 A	14-08-1996
		DK 11996 A	07-08-1996
		WO 9624595 A	15-08-1996
		EP 0808314 A	26-11-1997
		FI 960519 A	07-08-1996
		FR 2730232 A	09-08-1996
		GR 1002466 B	06-11-1996
		HK 59397 A	16-05-1997
		HU 9600255 A	28-03-1997
		IE 960104 A	07-08-1996
		IT MI960203 A	05-08-1997
		JP 8245620 A	24-09-1996
		LT 96007 A,B	25-10-1996
		LU 88711 A	23-08-1996
		LV 11618 B	20-04-1997
		MC 2411 A	02-12-1996
		NL 1002248 C	11-09-1996
		NL 1002248 A	06-08-1996
		NO 960472 A	07-08-1996
		NZ 280943 A	29-01-1997
		PL 312646 A	19-08-1996
		PT 101827 A,B	30-09-1996
		SE 9600406 A	07-08-1996
		SG 43787 A	14-11-1997

INTERNATIONAL SEARCH REPORT

..formation on patent family members

Inter ›nal Application No
PCT/GB 98/00081

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2297550 A		SI 9600036 A	31-10-1996
		SK 14396 A	06-11-1996
		NO 970939 A	07-08-1996

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 December 2002 (27.12.2002)

PCT

(10) International Publication Number
WO 02/102382 A1

(51) International Patent Classification[7]: A61K 31/445, C07D 405/12

(21) International Application Number: PCT/US02/19016

(22) International Filing Date: 14 June 2002 (14.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/298,603	14 June 2001 (14.06.2001)	US
60/326,993	5 October 2001 (05.10.2001)	US
60/346,048	4 January 2002 (04.01.2002)	US

(71) Applicant *(for all designated States except BB, US)*: **TEVA PHARMACEUTICAL INDUSTRIES LTD.** [IL/IL]; 5 Basel Street, P.O. Box 1390, 49131 Petah Tiqva (IL).

(71) Applicant *(for BB only)*: **TEVA PHARMACEUTICALS USA, INC.** [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **AVRUTOV, Ilya** [IL/IL]; 50 Beery Street, 42842 Bat Hefer (IL). **PILARSKI, Gideon** [IL/IL]; Ataroth 12/29, 58487 Holon (IL).

(74) Agents: **BRAINARD, Charles, R.**; Kenyon & Kenyon, One Broadway, New York, NY 10004 et al. (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/102382 A1

(54) Title: A PROCESS FOR PREPARING PAROXETINE HCl WHICH LIMITS FORMATION OF PINK COLORED COMPOUNDS

(57) Abstract: The present invention provides a process for preparing paroxetine HCl from paroxetine base which provides paroxetine HCl substantially free of pink-colored compounds or an impurity identified by an HPLC RRT of about 1.5. The processes of the present invention utilize a buffer, a molar ratio of HCl to paroxetine base of less than one, and crystallize/recrystallize in the presence of an effective amount of an anti-oxidant. A preferred way to create a buffer is by using ammonium chloride. A preferred anti-oxidant is ascorbic acid. The present invention also provides for re-crystallizing paroxetine HCl prepared by the above methods or any other methods in the presence of an effective amount of an anti-oxidant such as ascorbic acid. A preferred solvent system for recrystallization is a mixture of acetone and methanol. Processes of the present invention can combine these various features.

A PROCESS FOR PREPARING PAROXETINE HCl WHICH LIMITS FORMATION OF PINK COLORED COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

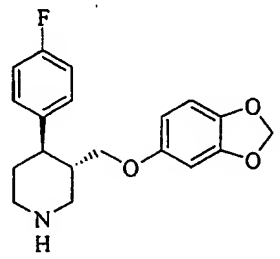
This application claims priority to provisional applications Serial No. 60/298,603, filed June 14, 2001; Serial No. 60/326,993, filed October 5, 2001 and Serial No. 60/346,048, filed January 4, 2002, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to paroxetine, more particularly, a process for the preparation of paroxetine HCl.

BACKGROUND OF THE INVENTION

Paroxetine, (-)-*trans*-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl) piperidine; (3S, 4R)-3-[5-(1,3-dioxaindanyl)oxymethyl]-4-(p-fluorophenyl)piperidine, is a 5-hydroxytryptamine (5-HT, serotonin) re-uptake inhibitor having the formula:



Paroxetine

Paroxetine, disclosed in U.S. Pat. No. 4,007,196, is prescribed for the treatment of, *inter alia*, depression, Parkinson's disease, anxiety disorders, obsessive-compulsive disorders, panic disorder and post-traumatic stress disorder. Other syndromes such as pre-menstrual syndrome (PMS) can also be treated with paroxetine. Paroxetine is marketed as Paxil® in dosage forms containing about 10-40 mg of paroxetine HCl.

A problem with paroxetine HCl tablets is that they often undergo a color change

over time. For example, U.S. Pat. No. 6,113,944, discloses that tablets of paroxetine HCl often develop an undesirable pink hue. The '944 patent discloses that formulations of paroxetine HCl prepared in an anhydrous environment have a less likelihood of developing a pink hue.

Without being bound by theory, it is believed that impurities in paroxetine hydrochloride play a role in the color change to pink. The level of the impurities in paroxetine that are associated with a color change to pink can be analyzed in two different manners. One approach is a simple visual analysis, *i.e.*, observing if a sample of paroxetine HCl has turned pink. Another approach is to measure the degree of an impurity identified by a high pressure liquid chromatography ("HPLC") relative retention time ("RRT") of about 1.5. The different UV-spectrum characteristic of this impurity has linked the impurity to the development of a pink color. A color change however can occur even if this impurity is present at low levels, suggesting that other impurities may also play a role in the color change. Purification steps to remove this impurity such as by crystallization, extraction, chromatography or other separation procedures are often ineffective.

Thus, there exists a need in the art to prepare paroxetine HCl and its formulations that do not undergo a color change, particularly to pink, during storage.

SUMMARY OF THE INVENTION

In one aspect, the present invention is directed to a process for preparing paroxetine HCl comprising reacting paroxetine base with less than one base equivalent of HCl, and separating the paroxetine HCl. The molar ratio of HCl to paroxetine base used is preferably from about 0.75 to about 0.95, more preferably from about 0.80 to about 0.90, and most preferably about 0.85

In another aspect, the present invention is directed to a process for preparing paroxetine HCl comprising converting paroxetine base to paroxetine HCl at a pH of greater than about 3.0, and separating the paroxetine HCl. Preferably, the pH is from about 3 to about 8.

In another aspect, the present invention is directed to a process for preparing paroxetine HCl comprising contacting paroxetine base with HCl in a buffer, and separating the paroxetine HCl. Preferably, a weak acidic reagent such as ammonium chloride is

added to create a buffer while HCl is added to complete the reaction.

In another aspect, the present invention is directed to a process for preparing paroxetine HCl comprising converting paroxetine base to paroxetine HCl and separating the paroxetine HCl, wherein at least a portion of the process occurrs in the presence of an effective amount of an anti-oxidant and optionally active carbon. A preferred anti-oxidant is ascorbic acid. A preferred amount of ascorbic acid used is from about 0.05 to about 10%, more preferably from about 0.10 to about 10% ascorbic acid (wt/wt% of ascorbic acid to paroxetine base). Preferably, the anti-oxidant is used in combination with active carbon.

In another aspect, the present invention is directed to a process for preparing paroxetine HCl comprising recrystallizing paroxetine HCl in the presence of an effective amount of an anti-oxidant and optionally active carbon, and separating the paroxetine HCl.

The various aspects of the present invention can be combined into a single process. For example, paroxetine base can be contacted with less than one base equivalent of HCl in the presence of a buffer, followed by crystallization in the presence of an anti-oxidant, and optionally active carbon. Alternatively, paroxetine HCl prepared by contacting paroxetine base with less than one base equivalent of HCl and an effective amount of anti-oxidant, can be re-crystallized in the presence of an effective amount of anti-oxidant.

A particularly preferred solvent for the processes of the present invention is toluene, and mixtures of toluene and PGME. A preferred solvent system for re-crystallization of crude paroxetine HCl is a mixture of acetone and methanol.

The present invention is also directed to paroxetine HCl prepared by the processes of and, pharmaceutical compositions thereof containing a pharmaceutically effective amount of paroxetine HCl and a pharmaceutically acceptable excipient, methods of administration thereof.

FIGURES

Figure 1 is the HPLC chromatogram for example 2.

Figure 2 is the HPLC chromatogram for example 3.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to novel processes for preparing paroxetine HCl which limit or prevent the formation of pink-colored compounds and/or the amount of an impurity identified by an HPLC RRT of about 1.5 by manipulating the equivalent ratio of HCl, using a buffer, using an anti-oxidant, or a combination thereof. The processes of the present invention limit the formation of impurities believed to be associated with a undesirable color change to pink, including an impurity identified by an HPLC RRT of about 1.5.

As used herein, "pink" has its ordinary meaning and refers to any of a group of colors reddish in hue, of medium to high lightness, and of low to moderate saturation. The term "rose" instead of "pink" is used synonymously in applications to which this application claims priority.

Paroxetine HCl is generally prepared by contacting paroxetine base with a slight excess of concentrated HCl. Such method for conversion however has drawbacks. The use of excess HCl without a buffer can lead to a rapid drop of pH to a pH of about 1 or less. Paroxetine has an acetal group (methylenedioxy), which can hydrolyze relatively easily under such strongly acidic conditions. Additionally, the use of an excess molar ratio of HCl can lead to deterioration of the final product. It is believed that the presence of excess HCl can accelerate acetal hydrolysis by becoming trapped in the final product.

The present invention provides processes designed to address the above drawbacks, thereby limiting the formation of impurities associated with an undesirable change of color to pink.

In one embodiment of the present invention, paroxetine HCl is prepared by contacting paroxetine base with HCl in a buffer. In this embodiment, a weak acid sets up a buffer while HCl is added at an equivalent of less than 1 to complete the conversion to the HCl salt. Preferably, the pH of the reaction mixture is greater than about 3, more preferably from about 3 to about 8.

As used herein, a "weak acid" refers to an acid that does not substantially completely ionize in water. A weak acid has a positive pKa. Ammonium ions, for example, which form as a result of dissociation of ammonium chloride in water, have a pKa of 9.24. An aqueous system employing a weak acid will typically have a pH of above about 3.

The reaction can be carried out by preparing a buffered aqueous solution, and a

solution of the base in an organic solvent. The two solutions are then mixed together. Depending on the miscibility of the organic solvent with the aqueous phase, a one or a two phase system is created. Preferably, a one phase system is obtained by using an organic solvent such as toluene that is miscible with the aqueous solution. The mixture of such organic solvents can also be used.

The aqueous solution is buffered by a weak acid. Ammonium chloride is a preferred weak acidic reagent. One of skill in the art can appreciate that ammonium chloride is a salt and its dissolution in an aqueous medium creates ammonium ions, which are the weakly acidic species.

When using a weak acidic reagent such as ammonium chloride, HCl is used to finish the reaction. Particularly when using ammonium chloride, ammonia builds up as the reaction proceeds, resulting in an increase in pH. The addition of HCl maintains a desired pH range.

The organic phase containing paroxetine base can be prepared by dissolving paroxetine base in an organic solvent, or a mixture of such solvents. Examples of such solvents include toluene and glycol monoethers. The use of toluene as a solvent is preferred due to a substantial difference in the solubility of paroxetine base and paroxetine HCl in toluene. Paroxetine base is substantially soluble in toluene, while paroxetine HCl is usually soluble in toluene only at high temperatures, such as reflux. The difference in solubility allows for the crystallization of the HCl salt upon formation thereof, facilitating the separation of the salt and further driving the equilibrium towards salt formation. Other preferred solvents include alcohols such as isopropanol.

Preferably, a mixture of toluene and glycol monoethers is used. The mixture used is preferably from about 8:1 to about 4:1 toluene to glycol monoethers, with a ratio of about 6:1 being preferred. The term "glycol monoethers" refers to the mono-(C_1-C_6, straight- or branched-chain)alkyl ethers of lower alkylene glycols such as, for example, ethylene glycol, propylene glycol, 1,3-butylene glycol and 2,3-butylene glycol. Among preferred glycol monoethers are, for example, ethylene glycol monomethyl ether ("methyl cellosolve", 2-methoxyethanol), ethylene glycol monoethyl ether ("ethyl cellosolve", 2-ethoxyethanol) and propylene glycol monomethyl ether ("PGME", 1-methoxy-2-propanol). Use of PGME is preferred.

After mixing of the two solutions, the base converts to the HCl salt and crystallizes

out of the mixture. The resulting mixture can be cooled to accelerate the crystallization of the HCl salt, preferably to a temperature of from about 0°C to about 10°C, more preferably to below about 5°C. The mixture can also be stirred, both to accelerate conversion to the HCl salt and to induce crystal formation.

The resulting crystals can then be separated by techniques well known in the art, such as filtration. After separation, the crystals can be washed, with an aqueous solvent such as water and a non-aqueous solvent such as toluene and then dried. The product can be dried from a temperature of from about 50°C to about 80°C. The pressure can be reduced to accelerate the drying process.

In another embodiment, paroxetine base is contacted with less than one base equivalent of HCl in the absence of a buffer. A solution of paroxetine base in an organic solvent or a mixture of solvents such as toluene and monoethers of glycol is prepared as described above. HCl is then added to the solution in a molar ratio of less than one to form paroxetine HCl. Preferably, the molar ratio of HCl to paroxetine base used is from about 0.75 to about 0.95 base equivalent, more preferably from about 0.80 to about 0.90, and most preferably about 0.85.

The solution can be cooled to accelerate the crystallization of the HCl salt, preferably to a temperature of from about 0°C to about 10°C, more preferably to below about 5°C. The resulting mixture can be stirred, both to accelerate conversion to the HCl salt and to induce crystal formation. If an aqueous medium is used, the pH of the reaction is preferably above about 3, more preferably from about 3 to about 8.

The resulting crystals can then be separated by techniques well known in the art, such as filtration. After separation, the crystals can be washed, with an aqueous solvent such as water and a non-aqueous solvent such as toluene and then dried. The product can be dried from a temperature of from about 50°C to about 80°C. The pressure can be reduced to accelerate the drying process.

In another embodiment, the HCl salt is prepared by carrying out at least a portion of the preparation of paroxetine HCl in the presence of an anti-oxidant. As used herein, an anti-oxidant has its ordinary meaning in the art and refers to a compound or a chemical substance that inhibits oxidation. One of skill in the art would appreciate that different anti-oxidants known in the art can be used with the present invention. The anti-oxidants used are preferably small organic molecules. Examples of such anti-oxidants include

ascorbic acid (Vitamin C), butylated hydroxytoluene (BHT), butylated hydroxyalanine (BHA), with ascorbic acid being preferred. An effective amount of ascorbic acid, preferably from about 0.05 to about 10%, more preferably from about 0.10 to about 10 % ascorbic acid (wt/wt% of ascorbic acid to paroxetine base) is used to provide paroxetine HCl product in accordance with the present invention. As one of skill in the art can appreciate, the preferred ratio of other anti-oxidants to paroxetine base can be determined in a routine fashion, with the preferred ratio for ascorbic acid being used as a guidance in such instance.

To crystallize the paroxetine HCl salt, HCl can be added to a solution of paroxetine base and an anti-oxidant in a suitable solvent. In a particularly preferred embodiment, HCl is added at a molar ratio of less than one base equivalent. Preferably, the molar ratio of HCl to paroxetine base used is from about 0.75 to about 0.95 base equivalent, more preferably from about 0.80 to about 0.90, and most preferably about 0.85.

A preferred solvent for the reaction is toluene. Other suitable solvents include alcohols. Preferably, in addition to an anti-oxidant, active carbon is added to the reaction mixture, which further improves decoloration. The amount of active carbon used is preferably from about 0.5 to about 1 gram of active carbon per about 100 ml of solution.

The reaction mixture can be stirred, and the temperature reduced to from about 0°C to about 10°C, more preferably to below about 5°C, to accelerate crystallization. The formed crystals can then be separated by techniques well known in the art, such as filtration. After separation, the crystals can be washed with toluene and water, and dried to give paroxetine HCl. The product can be dried from a temperature of about 50°C to about 80°C. The pressure can be reduced to accelerate the drying process. The paroxetine HCl so prepared can optionally be re-crystallyzed in the presence of an effective amount of an anti-oxidant and/or active carbon.

The anti-oxidant can be added at various times during preparation of paroxetine HCl. For example, the anti-oxidant can be present upon contacting paroxetine base with HCl or added after the conversion of the paroxetine base to paroxetine HCl. The presence of the anti-oxidant at least during crystallization of paroxetine HCl is preferred. Preferably, the anti-oxidant is introduced after the conversion to paroxetine HCl, but before crystallization of the HCl salt. In either case, the final product, *i.e.*, paroxetine HCl in solid form, is substantially free of anti-oxidants.

Crytallization in the presence of an anti-oxidant can be used in conjunction with the embodiments in which paroxetine HCl is prepared by using an HCl equivalent of less than one or the embodiment using a buffer, as described herein above. For example, paroxetine base and an effective amount of an anti-oxidant can be dissolved in an organic solvent such as toluene. The resulting solution can then be added to an aqueous solution containing a weak acid. HCl can then be added as described above in a ratio of less than about one base equivalent.

Paroxetine HCl can also be re-crystallized in the presence of an effective amount of an anti-oxidant such as ascorbic acid. To carry out the re-crystallization, paroxetine HCl is dissolved in a suitable organic solvent such as toluene. The toluene is preferably heated to reflux to increase its solubility for paroxetine HCl. Ascorbic acid, preferably with active carbon, is then added to the solution. If active carbon is added, it is subsequently removed, preferably by filtration.

After filtration, the filtrate can be cooled to a temperature of from about 0°C to about 10°C, with less than about 5°C being preferred, to accelerate the crystallization process. The crystals are then separated by techniques well known in the art, such as filtration. The crystals can then be washed with an organic solvent such as toluene and a non-organic solvent such as water.

The crude paroxetine HCl prepared by the embodiments of the present invention is preferably recrystallized in an acetone/methanol solvent system, optionally in the presence of an anti-oxidant. Paroxetine HCl is added to a mixture of acetone and methanol, preferably from about a 10:1 to about 30:1, more preferably about a 20:1 mixture. Preferably, an effective amount of ascorbic acid is also added to the mixture. The mixture can be heated, preferably to reflux, to form a solution. The solution is then passed through a charcoal bed to remove impurities. The filtrate is then cooled, preferably to slightly above 0°C, and a precipitate forms. The precipitate, paroxetine hydrochloride hemihydrate, is then separated by techniques well known in the art such as filtration and preferably dried. Two preferred schemes of the present invention are disclosed in Table-1.

Table-1--The schemes illustrated are similar, except scheme II does not use a buffer.

Preferred Scheme I	Preferred Scheme II
<1 molar equivalent of HCl	Same
ammonium chloride as a buffer	None

Crystallization in the presence of an effective amount of ascorbic acid	Same
Re-crystallization in the presence of an effective amount of ascorbic acid using a 20:1 mixture of acetone and methanol.	Same

The paroxetine hydrochloride of the present process is substantially free of impurities associated with a color change to pink, and is less susceptible, if at all, to develop a pink color overtime These impurities include the impurity identified by an HPLC RRT of about 1.5. Retention time refers to the time required for a compound to pass from the point of injection to the detector. Preferably, the processes of the present invention result in a final product having less than about 0.1% (HPLC area percentage) of the impurity identified by an HPLC RRT of about 1.5. After storage for at least four days at room temperature and a relative humidity of about 60-80%, the level of the impurity identified by an HPLC RRT of about 1.5 is preferably less than about 0.22, more preferably less than about 0.12 and most preferably less than about 0.02 (HPLC area percentage). HPLC area percentage refers to the sum of all the areas under the peak of an impurity in a chromatogram divided by the sum of all the areas under the peaks of all of the other compounds represented in the chromatogram.

The paroxetine hydrochloride of the present invention, in addition to analysis of the amount of the impurity identified by an HPLC RRT of about 1.5, can be analyzed visually for a color change. Preferably, the paroxetine HCl of the present invention remains substantially color-free upon long-term storage. In particular, the paroxetine HCl does not develop a pink color. The paroxetine HCl made in accordance with the present invention can be used to make storage-stable compositions which do not, or are substantially less susceptible, to becoming pink-colored during storage.

One visual analysis can be carried out by preparing a solution of about 2 mg/ml of paroxetine HCl prepared in a mixture of about 0.05M di-Potassium hydrogen phosphate buffer and about 35% of acetonitrile. If the product is substantially free of the impurities associated with a pink color, the solution does not develop a pink color after sitting for about 20 minutes. Preferably, the solution of the paroxetine HCl of the present invention is color free for at least about 20 minutes. On the other hand, available commercial products usually produce a pink colored solution under similar conditions.

Another visual analysis can be carried out by observing the color of paroxetine hydrochloride during storage. Preferably, the paroxetine HCl of the present invention is substantially free compounds associated with a pink color for at least four days at a temperature of about 55°C and a relative humidity of about 60-80%. One of skill in the art can appreciate that the level of the compounds associated with a pink color can vary according to the temperature and other conditions used for storage.

One of skill in the art can appreciate that the processes of the present invention can be used to prepare different forms of the HCl salt. The HCl salt of paroxetine exists in at least two solid state pseudopolymorph forms differentiated by their degree of hydration. Form I is a non hygroscopic hemihydrate and is thermodynamically more stable. Form II is a hygroscopic anhydrate. Form II converts to Form I if seed crystals of Form I are present, when exposed to humid conditions, or if subject to compression. Commercial paroxetine tablets such as Paxil® usually contain paroxetine HCl hemihydrate.

Paroxetine HCl also exists in other polymorphic forms and solvates of various different solvents. A particularly preferred solvate is the isopropanolate.

The processes of the prior art can be modified according to the teachings of the present invention to prepare the various forms of paroxetine HCl. Crude paroxetine HCl hemihydrate can be formed, for example, from a toluenic solution of paroxetine base by contacting the solution of paroxetine base with aqueous HCl followed by crystallization in an appropriate solvent as generally disclosed in U.S. Patent No. 4,721,723. Crystalline paroxetine HCl hemihydrate can then be prepared by recrystallization of the crude paroxetine HCl hemihydrate in a suitable solvent. Among suitable solvents are included, for example, lower alkanols such as methanol and ethanol; ketones such as acetone; esters such as ethyl acetate; and, mixtures of any of the foregoing such as methanol/acetone.

The prior art discloses various processes for preparing anhydrous forms of paroxetine HCl, as generally disclosed for example in U.S. Patent No. 6,080,759. The prior art discloses preparing anhydrous paroxetine HCl by contacting, in a dry N_2 environment, a solution of paroxetine base in an organic solvent, such as isopropanol, with dry HCl gas. Alternatively, the solution of paroxetine base in an organic solvent can be contacted with a solvent substantially free of water wherein the solvent has dry HCl gas dissolved therein. These prior art processes can be modified for crystallization in the presence of ascorbic acid or the use of a certain molar ratio of HCl.

Paroxetine hydrochloride anhydrate can be prepared via the hemihydrate or other solvates. As disclosed in U.S. Patent No. 6,080,759, anhydrate forms of paroxetine free of bound solvent can also be prepared from the paroxetine hemihydrate by dissolving the hemihydrate in an appropriate solvent substantially free of water which forms an azeotrope with water. Suitably, solvent is removed by distillation and fresh solvent is added until all of the water is removed.

Paroxetine HCl anhydrate can also be made by crystallizing paroxetine HCl in an organic solvent or a mixture of solvents which form a solvate with the paroxetine HCl and displacing the solvated solvent or solvents from the paroxetine HCl solvate using a displacing agent. Preferably, gaseous or liquid water can be used as the displacing agent. It is important that the paroxetine HCl solvate is contacted with enough water and for sufficient time to displace the solvent but insufficient to cause conversion to the HCl hemihydrate.

Paroxetine HCl can also be prepared in various solvate forms as disclosed in U.S. Pat. No. 6,080,759, the processes of which can be modified according to the teachings of the present invention. Among the preferred solvate forms is paroxetine HCl isopropanolate as disclosed for example in Examples 1-3 of U.S. Patent No. 6,080,759. Paroxetine HCl isopropanolate can be formed by displacing water from paroxetine HCl hemihydrate in, e.g., a mixture of toluene and isopropanol followed by crystallization. Paroxetine HCl isopropanolate can also be formed by contacting a solution of paroxetine base in isopropanol with dry HCl gas followed by crystallization. The isopropanolate can also be formed by contacting a solution of paroxetine base in dry isopropanol with a solution of dry HCl gas in dry isopropanol followed by crystallization. Solvates other than the isopropanolate can be made by similar methods as disclosed in U.S. Patent No. 6,080,759. Among such solvates are included solvates from solvents such as alcohols other than isopropanol such as 1-propanol and ethanol; from organic acids such as acetic acid; from organic bases such as pyridine; from nitriles such as acetonitrile; from ketones such as acetone and butanone; from ethers such as tetrahydrofuran; from chlorinated hydrocarbons such as chloroform and from hydrocarbons such as toluene. These solvates can be used to form the anhydrate forms free of bound solvent by either displacing the solvent as described above or by removing the solvent by conventional techniques such as vacuum oven drying.

The term paroxetein HCl as used in the present invention includes all these and other polymorphs, solvates and forms of paroxetine hydrochloride.

In accordance with the present invention, the highly pure forms of paroxetine HCl prepared by the new methods disclosed herein can be prepared as pharmaceutical compositions that are particularly useful for inhibiting the re-uptake of serotonin. Such compositions can include any of the various forms of the HCl salt in combination with pharmaceutically acceptable carriers and/or excipients known to one of skill in the art.

For example, these compositions may be prepared as medicaments to be administered orally, parenterally, rectally, transdermally, bucally, or nasally. Suitable forms for oral administration include tablets, compressed or coated pills, dragees, sachets, hard or gelatin capsules, sub-lingual tablets, syrups and suspensions. Suitable forms of parenteral administration include an aqueous or non-aqueous solution or emulsion, while for rectal administration suitable forms for administration include suppositories with a hydrophilic or a hydrophobic vehicle. For topical administration, suitable transdermal delivery systems known in the art, and for nasal delivery, suitable aerosol delivery systems known in the art, may be employed.

A particularly preferred unit dosage form is a coated tablet. Such tablet contains a pharmaceutically effective amount of the paroxetine HCl of the present invention in conjunction with one or more excipients, such as a binder, filler, stabilizer, disintegrant, glidant, flavoring and coloring agents. An effective amount of paroxetine HCl is approximately from about 10 mg to about 200 mg of the base equivalent of paroxetine HCl, as disclosed in U.S. Pat. No. 6,080,759, more preferably from about 10mg to about 100mg, and most preferably from about 10 to about 50 mg.

Suspensions, containing a dosage of about 10 mg of the base equivalent of paroxetine HCl per 5ml of liquid are also included within the scope of the pharmaceutical compositions of the present invention. The effective dose for the suspension is about the same as that for the tablet.

The prescribing information for Paxil® can be used as a guidance for both dosage and formulation of the paroxetine HCl of the present invention.

Instrumentation used

HPLC was performed on a XTERRA RP18 (5 um; 250 x 4.6 mm), reverse phase column with diammonium- hydrogen-phosphate buffer solution: acetonitrile mixture as gradient

eluent. Detected by U.V. spectroscopy at $\lambda = 285$ nm.

EXAMPLES

Example 1

Preparation of paroxetine HCl with a buffer

An aqueous solution of ammonium chloride (2 grams) in water (5ml) was added to a solution of paroxetine base (5 grams) in toluene (25ml). The reaction mixture was intensively stirred at ambient temperature while concentrated HCl was added in such manner that the pH of the reaction mixture stayed between 3.5 and 8. The stirring was continued for 1 hour. A precipitate formed which was filtered and then washed with toluene and water. The resulting material was dried at a temperature of 60°C under vacuum to give 4.9 grams of paroxetine HCl.

To test the purity of the final product, a 2 mg/ml solution of paroxetine HCl was prepared in a mixture of 0.05M di-Potassium hydrogen phosphate buffer and 35% of acetonitrile. The solution did not develop a pink color after standing for 20 minutes.

Example 2

Preparation of paroxetine HCl with a buffer and an HCl molar equivalent of less than 1

A solution of ammonium chloride (21.6 grams) in water (80 mL) was added to a solution of paroxetine base (53.2 grams), toluene (480 mL) and propyleneglycol monomethyl ether (PGME) (80 mL). HCl (15.7 grams, 0.85 equivalent, 32%) was then added. The mixture was cooled to 2-3°C, and stirred for 2.5 hours at this temperature (pH of water phase of reaction mixture was 7.5). The formed precipitate was filtered, washed with water and toluene, and dried at a temperature of 60°C under vacuum to give 48 grams of paroxetine. The content of the impurity at RRT about 1.5 after storage for 4 days at 55°C was .02.

Example 3

Preparation of paroxetine HCl without a buffer and an HCl molar equivalent of about 1

Example 2 was repeated, except the amount of HCl used was 18.5 grams (1

equivalent). The pH of the aqueous phase of the reaction mixture was about 1. The content of the impurity in the product (49.8 grams) after storage for 4 days at 55°C was 0.23.

Example 4

Preparation of paroxetine HCl in the presence of ascorbic acid

Concentrated HCl (2.43 grams) was added to a solution of paroxetine base (5.6 grams) and ascorbic acid (84 mg) in toluene (56 ml). The reaction mixture was stirred at room temperature for 30 minutes, and subsequently cooled to a temperature of 2-4°C. The mixture was kept at this temperature for about 1.5 hour. A precipitate formed. The formed precipitate was filtered, washed with toluene (5 ml) and water (5ml), and dried at 60°C under vacuum to give paroxetine HCl of white color (approximately 5 grams).

Example 5

Recrystallization of Paroxetine HCl in the presence of ascorbic acid and active carbon.

Paroxetine HCl (approximately 4 grams) was dissolved in toluene(40 ml) at reflux. Ascorbic acid (40 mg) and active carbon SX1 (200 mg) were added to the solution and stirred for 5-10 minutes. The solution was then filtered. The filtrate was cooled to 2-4°C, stirred for approximately 1 hour and filtered again to separate a formed precipitate. The solid precipitate was washed with toluene (4 ml) and dried at a temperature of 60°C under vacuum to give white (color-free) product (3.4 grams). The product was color-free during storage for at least one month at a temperature of 55°C, and yielded solutions (carried out in the same manner as example 1) that were also color-free.

Example 6

Preparation of Paroxetine HCl hemihydrate crystals

Paroxetine HCl crude (40g), acetone (400ml) and methanol (20ml) and ascorbic acid (0.2g) are added to a 1L flask. The mixture is heated to reflux, resulting in a solution. The stirring is continued for 15 minutes, after which the hot solution is filtered through a charcoal bed. The filter cake is washed with 5ml of a mixture acetone/methanol (20:1). The combined filtrates are cooled at 2-3°C and stirred for 1.5 hours. The precipitate is

filtered, washed with acetone (40ml) and dried to give 35g of paroxetine HCl hemihydrate crystals.

Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art can appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification. The Examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to, limit its scope in any way. The examples do not include detailed descriptions of conventional methods. Such methods are well known to those of ordinary skill in the art and are described in numerous publications. All references mentioned herein are incorporated in their entirety.

CLAIMS

What is claimed is:

1. A process for preparing paroxetine HCl comprising reacting paroxetine base with less than about one molar base equivalent of HCl and separating the paroxetine HCl, thereby providing a paroxetine HCl substantially free of pink-colored compounds or the amount of an impurity identified by an HPLC RRT of about 1.5.
2. The process of claim 1, wherein the ratio of the HCl to the paroxetine base is from about .75 to about .95 base equivalent.
3. The process of claim 2, wherein the ratio is from about .80 to about .90 base equivalent.
4. The process of claim 3, wherein the ratio is about .85 base equivalent.
5. The process of claim 1, wherein the reaction has a pH of from about 3 to about 8.
6. The process of claim 5, wherein the reaction takes place in a buffer.
7. The process of claim 6, wherein the buffer is a weak acid created by adding ammonium chloride to an aqueous medium.
8. The process of claim 1, wherein at least a portion of the process is carried out in the presence of an effective amount of an anti-oxidant and optionally active carbon.
9. The process of claim 8, wherein the anti-oxidant is ascorbic acid.
10. The process of claim 1, further comprising re-crystallizing the paroxetine HCl in the presence of an effective amount of an anti-oxidant and optionally active carbon.
11. The process of claim 10, wherein the anti-oxidant is ascorbic acid.
12. The process of claim 1, further comprising recrystallizing the paroxetine HCl from a mixture of methanol and acetone.
13. The process of claim 12, wherein the recrystalization is carried out in the presence of an effective amount of an anti-oxidant and optionally active carbon.
14. The process of claim 13, wherein the anti-oxidant is ascorbic acid.
15. The paroxetine HCl prepared by the process of claim 1.
16. A process of preparing paroxetine HCl comprising contacting paroxetine base with HCl at a pH of from about 3 to about 8, and separating the paroxetine HCl, thereby providing a paroxetine HCl substantially free of pink-colored compounds or the amount of an impurity identified by an HPLC RRT of about 1.5.

17. The process of claim 16, further comprising re-crystallizing the paroxetine HCl in the presence of an effective amount of an anti-oxidant and optionally active carbon.

18. The process of claim 16, further comprising re-crystallizing the paroxetine HCl from a mixture of acetone and methanol.

19. The process of claim 16 or 18, wherein at least a portion of the process is carried out in the presence of an effective amount of an anti-oxidant and optionally active carbon.

20. The process of claim 16, wherein molar ratio of the HCl used is less than about one base equivalent.

21. The paroxetine HCl prepared by the process of claim 16.

22. A process of preparing paroxetine HCl comprising contacting paroxetine base with HCl in a buffer and separating the paroxetine HCl, thereby providing a paroxetine HCl substantially free of pink-colored compounds or the amount of an impurity identified by an HPLC RRT of about 1.5.

23. The process of claim 22, wherein the reaction is buffered with a weak acid.

24. The process of claim 23, wherein the weak acid is a result of addition of ammonium chloride to an aqueous medium.

25. The process of claim 22, wherein the paroxetine base is contacted with less than about 1 molar equivalent of HCl.

25. The paroxetine HCl prepared by the process of claim 22.

26. A process for preparing paroxetine HCl comprising converting paroxetine base to paroxetine HCl, and separating the paroxetine HCl, wherein at least a portion of the process is carried out in the presence of an effective amount of an anti-oxidant, thereby providing a paroxetine HCl substantially free of pink-colored compounds or the amount of an impurity identified by an HPLC RRT of about 1.5.

27. The process of claim 26, wherein the anti-oxidant is selected from the group consisting of ascorbic acid, BHT and BHA.

28. The process of claim 27, wherein the amount of ascorbic acid used is from about 0.05% to about 10% weight of paroxetine HCl.

29. The process of claim 28, wherein the ascorbic acid is from about 0.1% to about 10% weight of paroxetine HCl.

30. The process of claim 26, wherein paroxetine base is converted to paroxetine HCl by contacting paroxetine base with less than about one base equivalent of HCl.

31. The process of claim 30, wherein the conversion takes place from a pH of from about 3 to about 8.

32. The process of claim 31, wherein the pH is buffered.

33. The process of claim 26, further comprising recrystallizing the paroxetine HCl in the presence of an effective amount of an anti-oxidant.

34. The process of claim 26, further comprising recrystallizing paroxetine HCl from a mixture of methanol and acetone.

35. The process of claim 34, wherein the re-crystallization is carried out in the presence of an effective amount of an anti-oxidant.

36. The paroxetine HCl prepared by the process of claim 26.

37. A process for preparing paroxetine HCl comprising the steps of:

a) reacting paroxetine base with less than about 1 molar equivalent of HCl in the presence of ammonium ions;

b) crystallizing the paroxetine HCl in the presence of an effective amount of an anti-oxidant and optionally active carbon;

c) separating the paroxetine HCl; and

d) re-crystallizing the paroxetine HCl, optionally in the presence of an anti-oxidant.

38. The process of claim 37, wherein the re-crystallization is carried out from a mixture of acetone and methanol.

39. The process of claim 37, wherein the anti-oxidant is ascorbic acid.

40. A process for preparing paroxetine HCl comprising the steps of:

a) reacting paroxetine base with less than about 1 molar equivalent of HCl;

b) crystallizing the paroxetine HCl in the presence of an effective amount of an anti-oxidant and optionally active carbon;

c) separating the paroxetine HCl; and

d) re-crystallizing the paroxetine HCl, optionally in the presence of an anti-oxidant.

41. The process of claim 40, wherein the re-crystallization is carried out from a mixture of acetone and methanol.

42. The process of claim 40, wherein the anti-oxidant is ascorbic acid.

43. Paroxetine HCl characterized by a having about 0.1% or less of an impurity identified by an HPLC RRT of about 1.5.

44. Paroxetine HCl characterized by less than about 0.22 of an impurity identified by an HPLC RRT of about 1.5 after storage for at least four days at a temperature of about 55°C, and that upon visual inspection does not appear pink.

45. The paroxetine HCl of claim 44, wherein the impurity is less than about .12

46. The paroxetine HCl of claim 45, wherein the impurity is less than about .02.

47. The paroxetine HCl of claim 43 or 44, wherein the paroxetine HCl does not appear pink upon visual inspection.

48. The paroxetine HCl of claim 43 or 44 wherein the paroxetine HCl is paroxetine HCl hemihydrate.

49. The paroxetine HCl of claim 43 or 44, wherein the paroxetine HCl is paroxetine HCl anhydrate.

50. The paroxetine HCl of claim 43 or 44, wherein the paroxetine HCl is a solvate of a solvent selected from the group consisting of isopropanol, 1-propanol, ethanol, acetic acid, pyridine, acetonitrile, acetone, butanone, tetrahydrofuran and toluene.

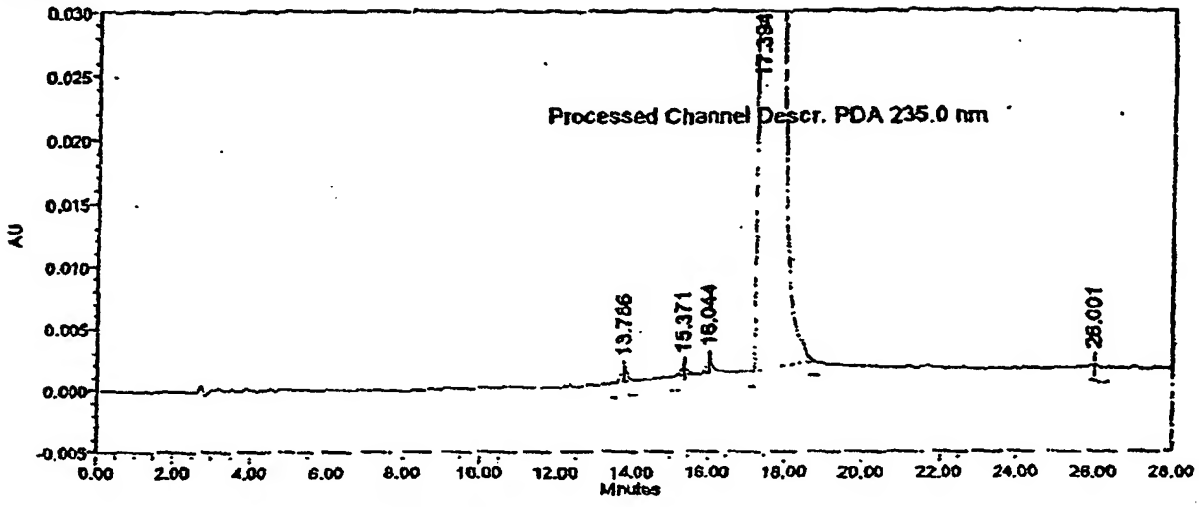
51. A pharmaceutical composition of paroxetine HCl comprising an effective amount of paroxetine HCl of claim 43 or 44, and a pharmaceutically acceptable excipient.

52. A method for inhibiting the re-uptake of serotonin in a mammal in need thereof comprising administering the pharmaceutical composition of claim 51.

53. A method for treating a disease or syndrome selected from the group consisting of depression, Parkinson's disease, anxiety disorders, obsessive-compulsive disorders, panic disorder, post-traumatic stress disorder and PMS comprising administering the pharmaceutical composition of claim 51.

Figure 1

Injection Volume 20.00 ul
Channel 996
Run Time 40.0 Minutes
Label



Peak Results

	Name	RT	Area	% Area	Height
1		13.786	11661	0.08	869
2		15.371	8580	0.06	586
3		16.044	11113	0.07	897
4		17.394	15346928	99.76	971551
5		26.001	2857	0.02	230

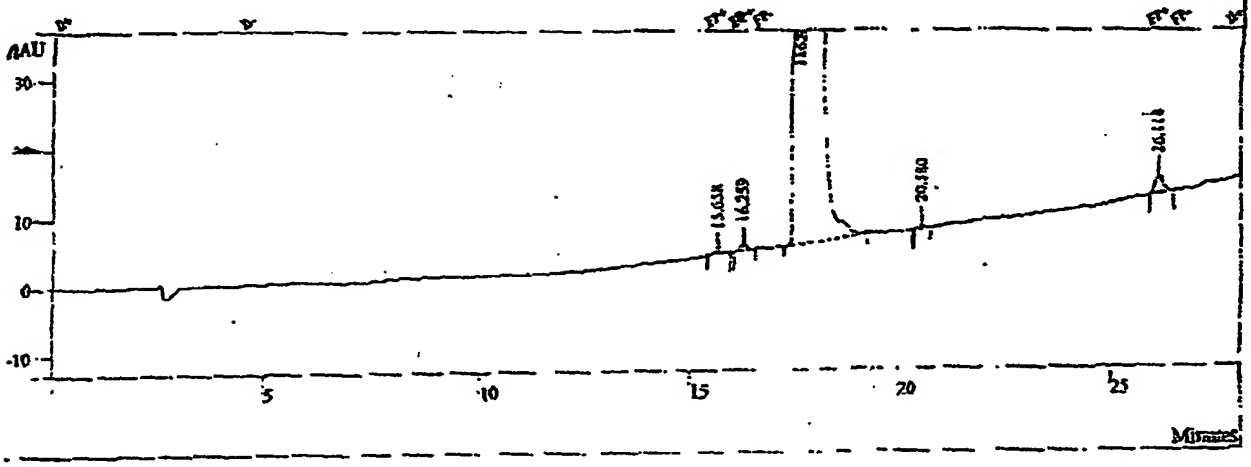
HPLC-1

Figure 2

Sample Prep Info

Loop Size: 20 ul Fill Volume: 20 ul Injection Volume: 20 ul

Run Time (min): 39.983
Sample Rate (Hz): 10.000
Detector Type: 9050



Peak No	Ret. Time (min)	Result ()	Peak Name	Area (counts)	Rel Ret Time	Sep. Code	Width 1/2 (sec)
1	15.658	0.052		3632	0.00	BB	15.4
2	16.259	0.072		5029	0.00	BB	13.7
3	17.626	99.609		6996793	0.00	BB	18.0
4	20.580	0.042		2920	0.00	BB	15.3
5	26.118	0.226		15886	0.00	BB	12.6
		100.001	Totals	7024260			

Status Codes:
U - User defined peak endpoint(s)

Peak Reject Value:	500.000	Multiplier:	1.000
Noise Before Run:	137 microAU	Divisor:	1.000
Noise Used:	137 microAU	Unident. Peak Factor:	0.000
Noise Source:	monitored before this run	Identified Peaks:	7024259
Rejected Peaks:	0	Unidentified Counts:	0
		Detected Peaks:	5

HPLC-2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/19016

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/445, C07D 405/12
US CL : 514/321, 546/197

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/321, 546/197

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CA 2,187,128 A1 [MURTHY ET AL] 04 April 1998(04.04.98), see entire documents, especially pages 3-6 examples.	15, 21, 25, 36, 43-53
Y	CA 2,193,939 A1 [MURTHY ET AL] 24 June 1998(24.06.98), see entire document, especially pages 3-5 examples.	15, 21, 25, 36, 43-53
Y	US 5,672,612 A [RONSEN ET AL] 30 September 1997(30.09.97), see entire document, especially col. 3-4 examples 1-2, claim 1.	15, 21, 25, 36,43-53
Y	EP 0,810,224 [ASAHI GLASS COMPANY LTD.] 30 May 1997(30.05.97), see entire document, especially column 3-4, examples 1-6.	15, 21, 25, 36, 43-53
X --- Y	WO 00/32593 A1 [SMITHKLINE BEECHAM PLC] 8 June 2000(08.06.00), see entire document, especially p.2 lines 12-17 and p.6, example 6.	1-7, 15, 16, 21, 22, 25, 43-53 --- 1-53
Y	WO 98/01424 A1 [RICHTER GEDEON VEGYESZETT GYAR RT] 15 January 1998(15.01.98), see entire document, especially22-23 example 22.	1-7, 15, 16, 21, 11, 25, 43-53
Y	US 4,721,723 [BARNES ET AL] 26 January 1988(26.01.88), see entire document, especially examples 1-7.	12, 18, 34, 38, 41
Y	US 5,872,132 A [WARD ET AL] 16 Feburary 1999(16.02.99), see entire document, especially column 4, lines 8-29 and examples.	12, 18, 34, 38, 41

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 September 2002 (11.09.2002)	03 OCT 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer Chang, Celia
Facsimile No. (703)305-3230	Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

PCT/US02/19016

INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/55698 A1 [SMITHKLINE BEECHAM PLC] 04 November 1999(04.11.99), see entire document.	8-11, 13-14, 17, 19, 27-29, 33, 35, 37, 39, 40, 42

INTERNATIONAL SEARCH REPORT

PCT/US02/19016

Continuation of B. FIELDS SEARCHED Item 3:
CAS--structure, paroxetine, ascorb?, impurity, color
EAST/WEST--subclass, image, paroxetine, ascorb$, impurity, color

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/445, 9/20 — A1

(11) International Publication Number: **WO 95/16448**

(43) International Publication Date: 22 June 1995 (22.06.95)

(21) International Application Number: PCT/EP94/04164

(22) International Filing Date: 14 December 1994 (14.12.94)

(30) Priority Data:
9325644.4 15 December 1993 (15.12.93) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: PATHAK, Ram, Dutta [GB/GB]; SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). DOUGHTY, David, George [GB/GB]; SmithKline Beecham Pharmaceuticals, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).

(74) Agent: RUSSELL, Brian, J.; Smithkline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PAROXETINE TABLETS AND PROCESS TO PREPARE THEM

(57) Abstract

Paroxetine which is formulated into tablets using a formulation process in which water is absent.

FOR THE PURPOSES OF INFORMATION ONLY

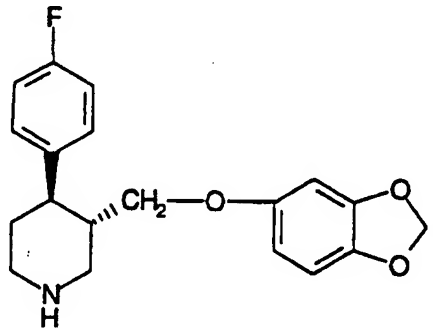
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

Paroxetine tablets and process to prepare them

The present invention relates to novel formulations and to the use of the formulation in the treatment and/or prevention of certain disorders.

US Patent 4,007,196 describes certain compounds which possess anti-depressant activity. One specific compound mentioned in this patent is known as paroxetine and which has the following formula:



This compound has been approved for human use and is being sold in many countries around the world as an anti-depressant agent.

It has been noticed that tablets of paroxetine often develop a pink hue which is highly undesirable.

To date, all tablets which have been sold have been formulated using an aqueous granulation process. It has surprisingly been found that formulation of paroxetine into tablets can be carried out reliably and on a commercial scale using a formulation process in which water is absent, such as by direct compression or by dry granulation.

It has also been surprisingly found that paroxetine formulated into a tablet using a process in which water is absent, is much less likely to develop a pink hue.

Accordingly, the present invention provides paroxetine which is formulated into tablets using a formulation process in which water is absent.

Examples of such a formulation process are dry direct compression of paroxetine or dry granulation of paroxetine followed by compression into tablets. The present invention therefore provides a formulation comprising direct compressed paroxetine admixed with dry excipients in the form of a tablet and a formulation comprising dry granulated and compressed paroxetine admixed with dry excipients in the form of a tablet.

It should be appreciated that the term "dry" means substantially "dry" as opposed to the wholesale addition of water which was previously employed in the wet granulation process.

Direct compression techniques are generally known in the art of pharmaceutical science. For example, paroxetine is conventionally admixed with dry excipients and compressed into tablets.

Dry granulation techniques are generally also known in the art of pharmaceutical science. For example, paroxetine is conventionally admixed with dry excipients and compressed into large slugs or roller compacted into ribbon-like strands. The compacted material is then suitably milled to produce a free flowing powder which is then compressed into tablets.

Additional excipients may then be added and mixed with the free flowing powder before being compressed into tablets.

Examples of excipients include calcium phosphate, microcrystalline cellulose, sodium starch glycollate and magnesium stearate which may be admixed in appropriate ratios.

It should be appreciated that particularly good results are obtained when microcrystalline cellulose is absent from the formulation, this is surprising as tablets formulated in the absence of microcystalline cellulose are often prone to breaking up during manufacture or storage.

The paroxetine/excipient mixture may be compressed into an appropriate tablet shape. Preferred shapes include a pentagonal circumcircle, oval, round bi-convex or a tilt-tablet such as those described in US Patent 4,493,822.

Paroxetine when incorporated into the above-mentioned tablets is suitably, present as the hydrochloride hemi-hydrate form which may be prepared according to the procedures outlined in US Patent 4,721,723.

The amount of paroxetine present in the above-mentioned tablets is in the range of 10 to 100 mg of paroxetine as measured in terms of the "free base". Particularly preferred amounts include 10 mg, 20 mg, 30 mg, 40 mg and 50 mg of paroxetine as measured in terms of the "free base". Particularly preferred amounts include 20 mg, 30 mg and 40 mg of paroxetine as measured in terms of the "free base".

Suitable procedures for preparing paroxetine include those mentioned in US Patents 4,009,196, 4,902,801, 4,861,893 and 5,039,803 and PCT/GB 93/00721.

It has been mentioned that paroxetine has particular utility in the treatment of depression, paroxetine may also be used in the treatment of mixed anxiety and depression, obsessive compulsive disorders, panic, pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia and the depression arising from pre-menstrual tension and adolescence.

The present invention therefore also provides a method of treating or preventing any of the above disorders which comprises administering an effective or

prophylatic amount to a sufferer in need thereof of paroxetine which is formulated into a tablet using a process in which water is absent.

The present invention further provides a pharmaceutical composition comprising paroxetine which is formulated into a tablet using a process in which water is absent for use in treating or preventing of the above disorders.

The present invention further provides the use of paroxetine which is formulated into a tablet using a process in which water is absent in the manufacture of a medicament for treating or preventing the above disorders.

The following examples illustrate the present invention:

Example 1

INGREDIENTS	**20 mg Tablet**	**30mg Tablet**
Paroxetine hydrochloride hemihydrate	22.67 mg	34.0 mg
Dicalcium Phosphate (DCP)	83.34 mg	125.0 mg
Microcrystalline Cellulose	50.67 mg	76.0 mg
Sodium Starch Glycollate	8.34 mg	12.5 mg
Magnesium Stearate	1.67 mg	2.5 mg
Tablet Weight	**166.7 mg**	**250.0 mg**

Commercial source of the ingredients

Dicalcium Phosphate Dihydrate	-	Emcompress or Ditab*
Microcrystalline Cellulose	-	Avicel PH 102*
Sodium Starch Glycollate	-	Explotab.*

* Tradenames

Method

1. Pass DCP through a screen and weigh it into a Planetary mixer.

2. Add 30 mesh Paroxetine to the bowl.

3. Add 20 mesh Avicel and Explotab and mix all the powders for 10 minutes.

4. Add magnesium Stearate and mix for 5 minutes.

Tablet into Pentagonal Tablets using the following punches:

30 mg Tablet	9.5 mm	Circumcircle
20 mg Tablet	8.25 mm	Circumcircle

The tablets are made satisfactorily on a single punch or a Rotary press.

Example 2

INGREDIENTS	10 mg Tablet	20 mg Tablet	30mg Tablet
Paroxetine hydrochloride hemihydrate	11.40 mg	22.80 mg	34.20 mg
Sodium Starch Glycollate	2.98 mg	5.95 mg	8.93 mg
Granular Dicalcium Phosphate (DITAB) or Dicafos	158.88 mg	317.75 mg	476.63 mg
Magnesium Stearate	1.75 mg	3.50 mg	5.25 mg
Tablet Weight	**175.00 mg**	**350.00 mg**	**525.00 mg**

Method

1. Paroxetine, Sodium Starch Glycollate and Dicalcium Phosphate Dihydrate are screened and mixed together in a suitable mixer. (Planetary, Cuble or High Energy Shear mixer.)

2. Add Magnesium Stearate and compress it into a tablet using a single punch or Rotary Tablet machine.

Claims

1. Paroxetine which is formulated into tablets using a formulation process in which water is absent.

2. A formulation process according to claim 1 which is a dry direct compression of paroxetine followed by compression into tablets or a dry granulation of paroxetine followed by compression into tablets.

3. A formulation process according to claim 1 or 2 in which paroxetine is admixed with dry excipients.

4. A formulation process according to claim 3 in which the paroxetine admixed with dry excipients is compressed into large slugs or roller compacted into ribbon-like strands.

5. A formulation process according to claim 4 in which the compressed or compacted material is milled to produce a free flowing powder and compressed into tablets.

6. A formulation process according to claim 3, 4 or 5 in which the excipients are selected from calcium phosphate, microcrystalline cellulose, sodium starch glycollate and magnesium stearate which may be admixed in appropriate ratios.

7. A formulation process according to claim 3, 4, or 5 in which microcrystalline cellulose is absent from the formulation.

8. A formulation process according to claim 5 in which the tablet is compressed into a pentagonal circumcircle, oval, round bi-convex, or tilt-tablet shape.

9. A formulation process according to any one of claims 1 to 8 in which paroxetine is in the form of the hydrochloride hemi-hydrate.

10. A formulation comprising direct compressed paroxetine admixed with any excipients in the form of a tablet.

11. A formulation comprising dry granulated and compressed paroxetine admixed with excipients in the form of a tablet.

12. A formulation according to claim 10 or 11 in which the excipients are selected from calcium phosphate, microcrystalline cellulose, sodium starch glycollate and magnesium stearate which may be admixed in appropriate ratios.

13. A formulation according to claim 10 or 11 in which the microcrystalline cellulose is absent.

14. A formulation according to any one of claims 10 to 13 in which the tablet is compressed into a pentagonal circumcircle, oral, round bi-convex or tilt-tablet shape.

15. A formulation according to any one of claims 10 to 14 in which the paroxetine is in the form of the hydrochloride hemi-hydrate.

Internat. Application No
PCT/EP 94/04164

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/445 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used) *

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 09281 (BEECHAM GROUP PLC) 11 June 1992 see claims see example 1	1-15
A	EP,A,0 269 303 (A/S FERROSAN) 1 June 1988 see claims see page 2, line 24 - line 50	1-15
A	EP,A,0 223 403 (BEECHAM GROUP PLC) 27 May 1987 see claims 1,4,5 see page 7, line 42 - line 55	1-15
A	EP,A,0 188 081 (A/S FERROSAN) 23 July 1986 see claims see page 2, line 21 - line 24	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 April 1995	21. 04. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Scarponi, U

Form PCT/ISA/210 (second sheet) (July 1992)

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9209281	11-06-92	AU-A-	8915391	25-06-92
		CA-A-	2096853	25-05-92
		EP-A-	0558679	08-09-93
		JP-T-	6502854	31-03-94
		US-A-	5371092	06-12-94
EP-A-0269303	01-06-88	AU-B-	601237	06-09-90
		AU-A-	8091787	12-05-88
		DE-A-	3786893	09-09-93
		DE-T-	3786893	03-03-94
		ES-T-	2058125	01-11-94
		IE-B-	59941	04-05-94
		JP-A-	63211228	02-09-88
		US-A-	4804669	14-02-89
EP-A-0223403	27-05-87	AU-B-	593295	08-02-90
		AU-A-	6433286	30-04-87
		CZ-A-	9103910	19-01-94
		DE-A-	3688827	09-09-93
		DE-T-	3688827	31-03-94
		ES-T-	2058061	01-11-94
		IE-B-	59901	20-04-94
		JP-B-	6047587	22-06-94
		JP-A-	62129280	11-06-87
		US-A-	4721723	26-01-88
EP-A-0188081	23-07-86	AU-B-	580820	02-02-89
		AU-A-	5074985	12-06-86
		DE-A-	3585607	16-04-92
		JP-C-	1881453	21-10-94
		JP-A-	61148121	05-07-86
		US-A-	4745122	17-05-88

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/445, 9/48 — A1

(11) International Publication Number: WO 99/26625

(43) International Publication Date: 3 June 1999 (03.06.99)

(21) International Application Number: PCT/GB98/03471

(22) International Filing Date: 18 November 1998 (18.11.98)

(30) Priority Data:
9724544.3 21 November 1997 (21.11.97) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: GHAZAWI, Ahmad [JO/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). LEONARD, Graham, Stanley [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: WEST, Vivien; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: FORMULATIONS COMPRISING DISSOLVED PAROXETINE

(57) Abstract

Pharmaceutical formulations of paroxetine are provided in which the paroxetine is in solution in a solid, semi–solid or liquid carrier. The solutions are used to fill capsules, or self–supporting solid solutions are shaped into solid dosage forms such as tablets or pellets. Also disclosed are novel liquid formulations in which a solubilising agent is used to solubilise paroxetine in oils and/or lipids, and methods of avoiding other paroxetine forms converting to the hemihydrate, by use of anhydrous or hydrophobic carriers or excipients.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

FORMULATIONS COMPRISING DISSOLVED PAROXETINE

The present invention relates to novel formulations of a pharmaceutically active compound, and to the use of the formulations in therapy. In particular this invention is concerned with new formulations of the anti-depressant paroxetine.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US-A-3912743 and US-A-4007196. An especially important compound among those disclosed is paroxetine, the (-)*trans* isomer of 4-(4'-fluorophenyl)-3-(3',4'-methylenedioxy-phenoxymethyl)-piperidine. Paroxetine hydrochloride hemihydrate is used in therapy for the treatment and prophylaxis of *inter alia* depression, obsessive compulsive disorder (OCD) and panic.

Paroxetine hydrochloride hemihydrate is described in EP-A-0223403 of Beecham Group and paroxetine hydrochloride anhydrate Forms A, B, C and D are described in WO 96/24595 of SmithKline Beecham plc. All solid oral dosage forms of paroxetine hydrochloride sold to date have been in the form of oral swallow tablets, containing the hemihydrate. WO 95/16448 discloses that paroxetine is likely to develop a pink colour unless it is formulated into tablets using a formulation process in which water is absent, such as dry direct compression of paroxetine or dry granulation of paroxetine followed by compression into tablets.

To assist in patient compliance with dosage regimes, there remains a need for alternative dosage forms to the swallow tablet. However, the low solubility of paroxetine hydrochloride in many solvents has made this difficult to achieve. In particular, it was not believed feasible to devise an oral swallow capsule of sufficiently small size to be readily swallowed and containing sufficient paroxetine in solution for an effective dose, using physiologically acceptable solvents capable of encapsulation. The present inventors have now overcome this problem.

In one aspect, the present invention provides an oral swallow capsule containing paroxetine dissolved in a carrier.

Typically the oral swallow capsule comprises a capsule shell containing paroxetine as the free base or a pharmaceutically acceptable salt or solvate thereof in solution in a carrier. The carrier may be liquid or solid.

A liquid carrier may be a solvent present in the capsule as a flowable liquid, as a viscous liquid or semi-solid or as a gel. The carrier may also be a solid or semi-solid solvent such as fats and waxes, or film-forming or thermoplastic polymers. Solvents in which supersaturated solutions can be formed are advantageous because of the possibility to increase the loading of active ingredient.

When the carrier is a solid or semi-solid or a gel, the paroxetine containing carrier may be self-supporting without encapsulation. Accordingly a self-supporting formulation may be encapsulated by other means than loading into a preformed capsule shell, for example by coating with an encapsulating material. Also the self-supporting formulation may be used as a dosage form without encapsulation.

Accordingly in another aspect the present invention provides an oral swallow solid dosage form containing paroxetine dissolved in a solid, semi-solid or gel carrier.

Typically the solid dosage form comprises tablets, pellets, spheroids, granules, lozenges or gels in which paroxetine is present as a solid solution in a polymeric carrier.

Capsules and solid dosage forms of this invention may be coated to assist in administration of the active ingredient, for example using an enteric coating material to prevent release of paroxetine in the stomach, coatings to delay or control release of paroxetine and coatings of taste-masking agents. Alternatively such materials can be incorporated in the carrier to achieve the same effect.

The paroxetine is preferably used as the hydrochloride, and as such may be used as the hemihydrate, or as the anhydrate Form A, B, C or D, or as any other form of paroxetine hydrochloride or paroxetine, such as pharmaceutically acceptable salts other than the hydrochloride. Other suitable paroxetine forms include paroxetine free base, and amorphous and non-crystalline forms of paroxetine and pharmaceutically acceptable derivatives of paroxetine.

In a particular embodiment, the capsules or solid dosage forms of present invention use paroxetine hydrochloride in a form other than the hemihydrate, and are formulated under conditions such there is no detectable conversion to hemihydrate during the manufacturing process.

This overcomes the surprisingly discovered problem that, even under relatively dry conditions, paroxetine hydrochloride anhydrate has a tendency to convert at least

partially to the hemihydrate during tabletting. Although not dangerous, this creates difficulties in establishing and maintaining a reference standard for regulatory and quality control purposes.

The paroxetine hydrochloride may, for example, be present in an amorphous form or as a crystalline anhydrate, and dissolved in a carrier, or in the presence of excipients, which are essentially hydrophobic, or essentially anhydrous, typically containing less than 2%, more especially less than 1.5%, preferably less than 1% by wt., water.

The amount of paroxetine used in each capsule is preferably adjusted such that in a single unit dose there is a therapeutically effective amount of paroxetine. Preferably the unit dose contains from 5 to 100 mg paroxetine (as measured in terms of the free base). More preferably the amount of paroxetine in a unit dose is 10mg, 20mg, 30mg, 40mg or 50mg. The most preferred amount of paroxetine in a unit dose is 20mg.

To achieve the desired unit dose in a capsule where the paroxetine is in solution in the carrier, the paroxetine needs to be soluble in the carrier to an extent that allows a sufficient concentration so that the selected capsule volume can contain the desired unit dose. In addition to being able to dissolve paroxetine, the solvent must be compatible with the capsule material and physiologically acceptable for administration to a patient.

Since solid paroxetine forms are in general only sparingly soluble in common solvents, the solvents which are acceptable for use in capsules and for administration to patients need to be subjected to routine solubility testing to confirm that they can maintain an appropriate concentration of paroxetine. In addition, higher loadings of a paroxetine form in a suitable solvent may be achieved by using conventional physical techniques such as heating, shaking and sonication. Alternatively good solvents for paroxetine may be used in small amounts as cosolvents to solubilize paroxetine in liquids that are acceptable for capsule use but in which paroxetine is poorly soluble. Solubilising agents such as the polysorbates, the poloxamers, cyclodextrins, ionic and non-ionic surface active agents, for example Pluronic F60 and Sorbitan esters may also be used to enhance the solubility of paroxetine hydrochloride in solvents acceptable for capsule use but in which paroxetine is poorly soluble.

The term "oral swallow capsule" most suitably denotes a capsule having a maximum volume of 0.86 ml . Preferred capsules according to the present invention have a maximum volume of about 0.45 ml and more especially may lie in the range 0.2 to 0.4 ml , although capsules as small as 0.14 ml are also provided by the invention. A typical

capsule at the upper end of the size range acceptable for pharmaceutical use (Soft Gel Size 14 Oblong) has a volume of 0.86 ml. For a 10 mg dose of paroxetine (as free base) 11.11 mg of paroxetine hydrochloride is needed, which in a volume of 0.86 ml requires a concentration of 12.9 mg/ml or 1.29 % w/v. Therefore it is preferred that the solvent which is used has a solubility of at least 10 mg/ml for paroxetine hydrochloride and more preferably the solubility should be at least 25 mg/ml. However larger capsule sizes such as Hard Shell Size 00 (0.95 ml capacity), Supro A (0.68 ml) and Softgel Size 12 Oblong (1.01 ml) may be used when appropriate to provide higher drug dose with the same formulation.

This level of solubility rules out many solvents conventionally used as liquid carriers for encapsulated drugs, such as the plant oils Sunflower, Safflower, Peanut, Soybean, Cottonseed, Corn, Castor, Apricot seed, Olive, Wheat germ, Sesame, Evening Primrose and Canola (Rapeseed) oil, and also Mineral oil and liquid paraffin. Other well known liquid carriers such as Miglyol (810 and 812), Oleic acid, Ethyl Oleate, Span 80 and 85, Labrafac lipophile, Plurol Oleique and Peceol (Glyceryl oleate) also show less than 10mg/ml solubility.

The present inventors have now identified certain solvents and solvent systems which exhibit the required levels of solubility. Solvents that show a useful solubility include Propylene Carbonate, Triacetin, Glycerol, Lauroglycol, Propylene glycol, PEG 300, Glycofurol, PEG 400, IPA, Span 20, Transcutol, Labrasol, Labrafil, Olepal, Glyceryl Linoleate (Maisine 35-1) and Pharmasolve. For physiological suitability it may be desirable to use such solvents with a cosolvent such as ethanol. The present invention makes use of these solvents and solvent systems as well as of functional equivalents thereof which can be identified using the techniques taught herein.

The present inventors have found that an especially effective means to solubilise paroxetine, particularly the hydrochloride, especially as the hemihydrate, in a liquid, semi-solid or solid carrier, in particular oils and lipids, is to use a solubilising agent, such as N-methyl-2-pyrrolidone (Pharmasolve, International Speciality Products, Texas, USA) as a cosolvent.

Accordingly in a preferred embodiment of this invention, paroxetine, optionally as the free base but more typically as a pharmaceutically acceptable salt such as the hydrochloride is dissolved in a solubilising agent and then blended with an oil or lipid carrier before filling capsules.

The invention also provides as a novel formulation a solution of paroxetine, optionally as the free base but more typically as a pharmaceutically acceptable salt such as the hydrochloride in a blend of a solubilising agent and a lipid and/or oil.

By use of a solubilising agent it is possible to solubilise paroxetine in oils and lipids previously regarded as unsuitable solvents, such as soybean oil, sunflower oil, and arachis oil.
Also by the same means paroxetine may dissolved in lipids, especially lipids derived from natural materials, such coconut oil-derived glycerides, Cithrol 4DL (PEG-8 dilaurate). Examples of coconut oil-derived glycerides include Labrasol and Labrafac CM10(Gattefosse, France) which are C_8/C_{10} polyglycolised glycerides from coconut oil having a hydrophilic:lipophilic balance of 14 and 10 respectively.

Formulations based on a solubilising agent and oils/lipids are preferably formulated with at least one antioxidant to maintain stability of the solution on storage. If it desired to use the solutions for filling capsules then the compatibility of the solution with the capsule material must be investigated.

The present invention in a further aspect makes use of supersaturated solutions, for example in solid or semi-solid solvents such as fats and waxes. These may readily be prepared by heating and exhibit high stability because of *inter alia* their very high viscosity.

Preferably, the solvents used in carrying out the invention contain less than 2%, more especially less than 1.5%, preferably less than 1%, water, or are essentially hydrophobic.

The solution may optionally contain one or more antioxidants such as the tocopherols, ascorbic acid, ascorbic palmitate, thiodipropionic acid, bis hydroxy toluene (BHT), bis hydroxy anisole (BHA), gallic acid, propyl/octyl/dodecyl gallate, benzyl alcohol and nordihydroguaiaretic acid with or without the addition of pH modifiers and chelating agents such as citric acid and EDTA.

The capsule shell may be of any conventional material that is stable to the liquid carrier and solute, for example hard and soft gelatin capsules and starch capsules. In addition to resisting the solvent action of the liquid carrier attention must be paid to the pH of the liquid within the capsule. For example soft gels have a pH limit of 2.5-7.5. Since the

addition of paroxetine hydrochloride to a solvent system tends to lower the pH by at least 1 unit, then in general solvent systems with a pH of below 3.5 are not preferred.

According to a further aspect of the invention, the capsules have an enteric resistant coating or incorporate enteric resistant materials in the capsule shell, such that the paroxetine is not discharged in the acidic conditions of the stomach. The object of this is to prevent any undesired uncontrolled precipitation of the paroxetine from solution, and to enable its absorption characteristics to be modified if desired by presenting it to the intestinal mucosa in non-aqueous solution.

The liquid carrier may be present in the capsule as a flowable liquid, as a viscous liquid or semi-solid or as a gel. The viscosity characteristics may be varied by initial choice of solvent or by appropriate use of cosolvents or thickening agents.

A liquid carrier, or a solid or semi-solid carrier that has been softened or made flowable by heating, with dissolved paroxetine may be filled into capsules using conventional capsulation technology.

It may be desirable to use paroxetine hydrochloride in a form other than the hemihydrate, which is formulated into capsules or solid dosage forms under conditions such there is no detectable conversion to hemihydrate during the manufacturing process. The paroxetine hydrochloride may, for example, be present in an amorphous form or as a crystalline anhydrate.

This may be achieved for example by the use of either excipients or carriers which are essentially anhydrous (that is to say, they contain less than 2%, more especially less than 1.5%, preferably less than 1% water) or which are essentially hydrophobic. The capsules and solid dosage forms are then preferably packaged with a desiccant in order to prevent conversion of anhydrate to hemihydrate on storage.

Accordingly, the present invention also provides a process for the preparation of paroxetine hydrochloride anhydrate capsules or solid dosage forms free of detectable hemihydrate which is characterised by the use of conditions such there is no detectable conversion of the anhydrate to hemihydrate during the manufacturing process. Such conditions can be achieved by the use of essentially anhydrous/hydrophobic excipients and/or carriers under conditions of low relative humidity

Examples of excipients with the necessary low moisture content include materials such as dibasic calcium phosphate anhydrous, anhydrous lactose, monosaccharide sugars eg mannitol, disaccharide sugars eg lactitol, powdered cellulose, pregelatinised starch and similar materials. Dibasic calcium phosphate anhydrous is commercially available in a pharmaceutically acceptable grade, eg A-TAB (Rhone Poulenc).

Examples of liquid and semi-solid excipients with the necessary hydrophobicity include materials such as polyglycolised glycerides eg Gelucire 44/14; complex fatty materials of plant origin eg theobroma oil, carnauba wax; plant oils eg peanut, olive, palm kernels, cotton, corn, soya; hydrogenated plant oils eg peanut, palm kernels, cotton, soya, castor, coconut; natural fatty materials of animal origin eg beeswax, lanolin, fatty alcohols eg cetyl, stearyl, lauric, myristic, palmitic, stearic; esters eg glycerol stearate, glycol stearate, ethyl oleate, isopropyl myristate; solid interesterified semi-synthetic glycerides eg Suppocire, Witepsol; liquid interesterified semi-synthetic glycerides eg Miglyol 810/812,; amide or fatty acid alcolamides eg stearamide ethanol, diethanolamide of fatty coconut acids; polyoxyethylene glycols eg PEG 600, PEG 4000.

Liquids and semi-solids having suitable solubility characteristics to act as carriers for dissolved paroxetine, and having similar hydrophobicity to the above liquid excipients, include Labraphil, a liquid interesterified semi-synthetic glyceride, and PEG 400, a polyoxyethylene glycol.

The above solid and liquid excipients may be blended with carriers of suitable solubility for paroxetine disclosed above and if necessary cosolvents to obtain solutions of paroxetine with anhydrous/hydrophobic properties. Carriers already having suitable anhydrous/hydrophobic properties may be blended directly with paroxetine, again using cosolvents where neccessary to promote dissolution. The formulations may be filled into capsules, such as gelatin capsule shells, or cellulose capsule shells of intrinsically low moisture content (eg Shionogi Qualicaps, < 3%).

Liquid interesterified semi-synthetic glycerides commercially available in a pharmaceutically acceptable grade include Labrafil M 2125CS (Gattfosse). In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with Labrafil M 2125CS (Gatfosse) to produce a formulation for encapsulation in a hard or soft gelatin capsule.

Paroxetine in the form of the hydrochloride anhydrate may be prepared according to the procedures outlined in WO 96/24595. Suitable procedures for preparing paroxetine include those mentioned in US Patents 4,009,196, 4,902,801, 4,861,893 and 5,039,803 and PCT/GB 93/00721.

The present invention also provides solid dosage forms of paroxetine for oral swallow use in which paroxetine is dissolved in a polymeric carrier. These forms include tablets, pellets, spheroids, granules, lozenges and gels containing paroxetine in solid solution.

To achieve the desired unit dose in for example a melt extruded tablet where the paroxetine is in solution in the polymer carrier, the paroxetine needs to be soluble in the polymer carrier or a solvent/cosolvent that is soluble in the polymer carrier to an extent that allows a sufficient concentration so that the selected tablet size and volume can contain the desired unit dose. In addition to being able to dissolve paroxetine, the solvent/cosolvent must be compatible with the polymer carrier material and physiologically acceptable for administration to a patient.

When the solid dosage form is granules or pellets then a plurality of granules or pellets may be collected in an aggregation that as a whole constitutes a unit dose. The granules or pellets may be used as a fill for capsules or pressed, optionally with binders or excipients, into tablet form.

Since solid paroxetine forms are in general only sparingly soluble in common solvents, the solvents/co-solvents and carriers which are acceptable for use in the above dosage forms and for administration to patients need to be subjected to routine solubility testing to confirm that they can maintain an appropriate concentration of paroxetine. In addition, higher loadings of a paroxetine form in a suitable solvent may be achieved by using conventional physical techniques such as heating, shaking and sonication. Alternatively good solvents for paroxetine may be used in small amounts as cosolvents to solubilize paroxetine in polymers that are acceptable for melt extrusion, melt granulation, gel formulation use but in which paroxetine is poorly soluble. Solubilising agents such as the polysorbates, the poloxamers, cyclodextrins, ionic and non-ionic surface active agents, for example Pluronic F60 and Sorbitan esters may also be used to enhance the solubility of paroxetine hydrochloride in solvents acceptable for polymers used to produce solid solution systems in forms of tablet, pellet, granule, spheroid use but in which paroxetine is poorly soluble.

It is preferred that the polymer and/or solvent which are used have a solubility of at least 10 mg/ml for paroxetine hydrochloride and more preferably the solubility should be at least 25 mg/ml.

In general the use of polymers in this invention to produce semi-solid/solid solution system offer a broad flexibility of use. Beside filling into hard/soft gelatin capsules they may be used to make melt extruded system such as tablets, pellets, spheroid and any other shape depending on the shape of the extruder die, can be injection moulded into different shapes and /or melt granulated to produce pellets or granules. Alternatively the granules can be milled and pressed into tablets and other shapes depending on the shape and design of the press die.

Examples of the pharmaceutical polymers used for the above applications are film forming and thermoplastic polymers that are generally approved substances listed in international Pharmacopoeias such as polyethylene oxide water soluble resins, ethoxylated glycerides and triglycerides, cetyl esters, cetyl palmitate, glyceryl esters, polyvinyl acetate, cellulose, lanolin based product, vinyl resins, latex product, carbowax polyethylene glycols, gelatin (protein), ethylene oxide/glycol such as ethylene glycol, glycol ethers and ethanolamines, unipol polymers, polypropylene resins, silicone products, saturated polyglycolysed glycerides, glyceryl behenate, glyceryl palmitostearate, semisynthetic glycerides and vinyl acetate monomers. The function(s) of these polymers will be as a drug carrier and/or solubiliser and/or binder and/or permeability enhancers.

Solvents that show a useful solubility for paroxetine, such as Propylene Carbonate, Triacetin, Glycerol, Lauroglycol, Propylene glycol, PEG 300, Glycofurol, PEG 400, IPA, Span 20, Transcutol, Labrasol, Labrafil, Olepal, Glyceryl Linoleate (Maisine 35-1) and Pharmasolve mentioned previously, may be used as cosolvents to assist solubilisation of paroxetine in the solide, semi-solid and polymeric carriers mentioned above. For physiological suitability it may be desirable to use such solvents with another cosolvent such as ethanol. The present invention makes use of these solvents and solvent systems as well as of functional equivalents thereof which can be identified using the techniques taught herein.

An appropriate lanolin derivative e.g. ethoxy-75 lanolin is commercially available in a pharmaceutical grade e.g. Solan E (Croda). In a particular process of the invention, paroxetine hydrochloride hemihydrate is dissolved in Pharmasolve and mixed with

molten Solan E in a suitable blender to form granules on cooling, drying, sifting then solid solution tablet upon compression.

A polyglycolised glyceride is commercially available in a pharmaceutically acceptable grade .e.g. Gelucire 44/14 (Gattfosse). In a particular process of the paroxetine invention, paroxetine hydrochloride hemihydrate is dissolved in Pharmasolve and then mixed with molten Gelucire 44/14 to form a melt extrudate in forms of a tablet and/or pellet on cooling.

Polyethylene glycols of different molecular weights are commercially available in a pharmaceutically acceptable grade e.g. PEG 4000 (Union Carbide Corp & BASF). In a particular process of the invention , Paroxetine hydrochloride hemihydrate is dissolved in PEG 300 and then mixed with molten PEG 4000 to form melt extruded materials which on cooling as solid solution may be converted into forms of tablets and/or pellets.

The solid solution may optionally contain one or more antioxidants such as the tocopherols, ascorbic acid, ascorbyl palmitate, thiodipropionic acid, bis hydroxy toluene (BHT), bis hydroxy anisole (BHA), gallic acid, propyl/octyl/dodecyl gallate, benzyl alcohol and nordihydroguaiaretic acid with or without the addition of pH modifiers and chelating agents such as citric acid and EDTA.

According to a further aspect of the invention, the solid dosage form may have an enteric resistant coating such that paroxetine is not discharged in the acidic conditions of the stomach. The object of this is to prevent any undesired uncontrolled precipitation of the paroxetine from solution, and to enable its absorption characteristics to be modified if desired by presenting it to the intestinal mucosa in an aqueous solution.

The solid solution/semi-solid systems presented in this invention can be coated with suitable polymer that can be used with melt granulation or hot melt coating such as Precirol ATO 5 (Glyceryl palmito stearate) for taste-masking paroxetine and/or enterically coated with methacrylic acid copolymer C (e.g. Eudragit L 30 D-55).

The semi-solid or gel formulation can also be optionally capsulated. The viscosity characteristics of the semi-solid or gel may be varied by initial choice and amount of solvent or by appropriate use of cosolvents or thickening agents.

The semi-solid or gel carrier with dissolved paroxetine may be filled into capsules using conventional capsulation technology.

Self-supporting solid of paroxetine solution can be successfully prepared in forms of tablet, pellets, spheroid, granules using Solan E, Gelucire, higher molecular weights of PEG's and gel based on gelatin with different cosolvents constituents.

For example, the paroxetine is first dissolved in co-solvent constituents, such as PEG 300, Pharmasolve and water/ethanol (using sufficient mixing to assure complete wetting/solubilisation). The resultant mixture is then preheated and added to a suitable portions of a melted polymer such as Gelucire 44/14 (melting point 42-46 C), Solan E (melting point 45-50 C), PEG 6000 (melting point 55-63 C), PEG 4000 (melting point 50-58 C) or Gelatin (gelatin in liquid co-solvents melted between 50-55 C). The samples may then be left at ambient condition for resolidification of the polymer to occur. A shaping device may then be used to produce solid dosage forms as tablets, pellets, spheroids and gels. The drug molecule dissolved in the polymer during the melting phase will remain dissolved in the finished product as a solid solution. With gelatin based formulations, transparent solid solutions containing dissolved drug are produced.

As mentioned above, itt may be desirable to use paroxetine hydrochloride in a form other than the hemihydrate, which is formulated into self-supporting solid dosage forms under conditions such there is no detectable conversion to hemihydrate during the manufacturing process. The paroxetine hydrochloride may, for example, be present in an amorphous form or as a crystalline anhydrate.

As already described, this may be achieved for example by the use of either excipients or polymeric carriers which are essentially anhydrous (that is to say, they contain less than 2%, more especially less than 1.5%, preferably less than 1% water) or which are essentially hydrophobic.

Therapeutic uses of the paroxetine formulations of this invention include treatment of: alcoholism, anxiety, depression, obsessive compulsive disorder, panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, pre-menstrual syndrome (PMS), adolescent depression, trichotillomania, dysthymia, and substance abuse, referred to below as "the disorders".

Accordingly, the present invention also provides:

the use of paroxetine dissolved in a carrier to manufacture oral swallow capsules or solid dosage forms for the treatment or prophylaxis of one or more of the disorders;

a method of treating the disorders which comprises administering an effective or prophylactic amount of paroxetine as a solution in a carrier in an oral swallow capsule or solid dosage form to a person suffering from one or more of the disorders;
a method of treating the disorders which comprises administering an effective or prophylactic amount of paroxetine as a solution in a liquid formulation of the invention to a person suffering from one or more of the disorders.

The formulations of this invention may also be used where appropriate for veterinary treatment of animals.

The invention is illustrated by the following Examples:
(Paroxetine anhydrous free base 10.0 mg is equivalent to 11.38 mg paroxetine HCl - conversion factor from paroxetine HCl to paroxetine anhydrous base is 0.8787).

In Examples 1 - 10, paroxetine is dissolved in a carrier, optionally assisted by a cosolvent, and filled into capsules.

Example 1.	Excipient	mg per capsule
	Paroxetine hydrochloride	22.22
	Polyethylene Glycol 400	450.0
Capsule	Size 11 Oblong Soft Gel	

Example 2.	Excipient	mg per capsule
	Paroxetine hydrochloride	22.22
	Polyethylene Glycol 400	400.0
	Ethanol	45.0
Capsule	Size 0 Hard Shell, banded	

Example 3.	Excipient	mg per capsule
	Paroxetine hydrochloride	22.22
	Propylene Glycol	350.0
Capsule:	Size 8 Oblong Soft gel	
Enteric Coat	Methacrylic Acid Copolymer Type C	32.0
	Propylene Glycol	8.0

Example 4.	Excipient	mg per capsule
	Paroxetine hydrochloride	22.22
	Fractionated coconut oil	300.0
	Polyethylene Glycol 400	150.0
	Polysorbate 80	50.0
Capsule:	Size 11 Oblong Soft gel	

Example 5.	Excipient	mg per capsule
	Paroxetine hydrochloride	22.22
	Glycerol	100.0
	Propylene Glycol	100.0
	Propyl gallate	0.3
Capsule:	Size 5 Oblong Soft gel	

Example 6.	Excipient	mg per capsule
	Paroxetine hydrochloride	22.22
	Glycofurol	100.0
	Polyethylene glycol 300	50.0
	Citric acid	1.5
	BHT	0.02
Capsule:	Size 4 Oblong Soft gel	

Example 7.	Excipient	mg per capsule
	Paroxetine hydrochloride	22.22
	Pharmasolve	50.0
	High Purity Cotton Seed Oil	150.0
	Propyl gallate	0.2
Capsule:	Size 4 Oblong Soft gel	

Example 8.	Excipient	mg per capsule
	Paroxetine hydrochloride	22.22
	Polyethylene Glycol 400	50.0
	Pharmasolve	10.0
	Citric Acid	2.0
Capsule	Size 3 Oval Soft Gel	

Example 9.	Excipient	mg per capsule

	Paroxetine hydrochloride	22.22
	Lauroglycol 400	100.0
	Pharmasolve	10.0
	Citric Acid	2.0
Capsule	Size 3 Hard Shell, banded	

Example 10.	Excipient	mg per capsule
	Paroxetine hydrochloride	22.22
	Polyethylene Glycol 400	50.0
	Pharmasolve	10.0
	Citric Acid	2.0
Capsule	Starch Capil	

In Example 11, paroxetine is dissolved in a hydrophobic carrier.

Example 11	**mg**
Paroxetine hydrochloride †	22.22
Labrafil M 2125CS	227.78
Capsule weight	250.00

In Examples 12-30, paroxetine was dissolved in a cosolvent, and then blended with a molten polymer. Clear paroxetine solutions were obtained before solidification of the polymers.

Example 12	Paroxetine HCL	22.76 mg
	PEG 300	200.00 mg
	PEG 4000	300.00 mg
	dl alfa tocopherol	0.1% w/w
Tablet	Ascorbyl Palmitate	0.1% w/w
Example 13	Paroxetine Hydrochloride	45.52 mg
	Gelucire 44/14	227.78 mg
Tablet	Pharmasolve	100.00mg
Example 14	Paroxetine Hydrochloride	22.76 mg
Tablet	Gelucire 44/14	227.78 mg
Example 15	Paroxetine Hydrochloride	68.28 mg
	Solan E (ethoxy 75 lanolin)	350.00 mg
Tablet	Pharmasolve	150.00mg

Example 16	Paroxetine Hydrochloride	22.76 mg
Tablet	PEG 1450	227.78 mg
Example 17	Paroxetine Hydrochloride	22.76 mg
Tablet	PEG 4000	227.78 mg
Example 18	Paroxetine HCL	19.91 mg
	PEG 300	200.00 mg
	PEG 1450	300.00 mg
	dl alfa tocopherol	0.1% w/w
Tablet	Ascorbyl Palmitate	0.1% w/w
Example 19	Paroxetine Hydrochloride	22.76 mg
Tablet	Suppocire DM	227.78 mg
Example 20	Paroxetine HCL	73.96 mg
	Gelatine	100.00 mg
	Purified water	350.00 mg
	Pharmasolve	150.00 mg
	Polysorbate 80	1 drop
Gel	Methyl Paraben	0.2% w/w
Example 21	Paroxetine HCL	42.67 mg
	Gelatine	50.00 mg
	Purified water	200.00 mg
	Propylene Glycol	400.00 mg
	Propyl Gallate	0.1% w/w
	Ascorbic Acid	0.1% w/w
Gel	Polysorbate 80	1 drop
Example 22	Paroxetine HCL	113.79 mg
	Gelatine	50.00 mg
	Purified water	200.00 mg
	Pharmasolve	200.00 mg
	Propylene Glycol	200.00 mg
	Polysorbate 80	1 drop
Gel	Methyl Paraben	0.2% w/w
Example 23	Paroxetine HCL	102.41 mg
	Gelatine	50.00 mg
	Purified water	200.00 mg
	Pharmasolve	200.00 mg
	Ethanol	200.00 mg
	Polysorbate 80	1 drop

Gel	Methyl Paraben	0.2% w/w
Example 24	Paroxetine HCL	28.45 mg
	Gelatine	50.00 mg
	Purified water	200.00 mg
	Ethanol	200.00 mg
	Propylene Glycol	200.00 mg
Gel	Polysorbate 80	1 drop
Example 25	Paroxetine HCL	45.52 mg
	Gelatine	50.00 mg
	Purified water	200.00 mg
	Propylene Glycol	400.00 mg
	PEG 300	50.00 mg
Gel	Polysorbate 80	1 drop
Example 26	Paroxetine HCL	11.38 mg
	Gelatine	50.00 mg
	Purified water	500.00 mg
	Propylene Glycol	100.00 mg
Gel	Polysorbate 80	1 drop
Example 27	Paroxetine HCL	28.45 mg
	Gelatine	50.00 mg
	Purified water	300.00 mg
	Propylene Glycol	300.00 mg
Gel	Polysorbate 80	1 drop
Example 28	Paroxetine HCL	68.28 mg
	Gelatine	50.00 mg
	Purified water	300.00 mg
	Pharmasolve	150.00 mg
	Propylene Glycol	150.00mg
Gel	Polysorbate 80	1 drop
Example 29	Paroxetine HCL	79.65 mg
	Gelatine	50.00 mg
	Purified water	300.00 mg
	Pharmasolve	150.00 mg
	Ethanol	150.00 mg
	Polysorbate 80	1 drop
Gel	Methyl Paraben	0.2% w/w
Example 30	Paroxetine HCL	17.07 mg
	Gelatine	50.00 mg
	Purified water	300.00 mg
	Propylene Glycol	150.00 mg
	Ethanol	150.00 mg

Gel Polysorbate 80 1 drop

In Examples 31 - 44, paroxetine is initially dissolved in Pharmasolve and the resultant solution is blended with oil and lipid carriers, so that the paroxetine is dissolved in the carrier to give liquid formulations that may be capsulated (36 - 42) and also provided with an enteric coating (43 - 45)

	Composition	Appearance of System/Solution^	Stability of Pxt solution *
Example 31	Labrasol.....2.25mL Pharmasolve....0.25mL Drug 125mg	clear pale yellow solution	clear very pale pink solution
Example 32	Cithrol 4DL.....2.25mL Pharmasolve....0.25mL Drug 125mg	clear pale yellow solution	clear pale pink solution
Example 34	Sunflower oil....2.25mL Pharmasolve....0.25mL Drug.....125mg	clear pale yellow solution	no change clear v. pale yellow solution
Example 35	Soybean oil.....2.25mL Pharmasolve....0.25mL Drug.....125mg	clear pale yellow solution	no change clear pale yellow solution
Example 36	Arachis oil.....2.25mL Pharmasolve....0.25mL Drug.....125mg	clear pale yellow solution	no change clear v. pale yellow solution

* stored at RT for 25 days (visual observation)

^ at the time of preparation (fresh samples)

Example	Composition	Appearance of System/Solution^	Stability of Pxt solution*	Compatability with Licaps Capsule*
36	Labrafac CM10.....4.50mL Pharmasolve.....0.50mL	clear pale	clear pale	Yes

	Tween 80.....1 drop Drug.....250mg	yellow solution	yellow solution	

37	Labrafil M 1994Cs.....4.50mL Pharmasolve.....0.50mL Tween 80.....1 drop Drug.....250mg	clear pale yellow solution	yellow viscous/semi solid	Yes
38	Labrasol.....4.50mL Pharmasolve.....0.50mL Tween 80.....1 drop Drug.....250mg	clear pale yellow solution	clear pale yellow solution	Yes
39	Cithrol 4DL.....4.50mL Pharmasolve.....0.50mL Tween 80.....1 drop Drug.....250mg	clear pale yellow solution	clear v. pale pink solution	Yes

* stored at RT for 10 days (visual observation)

^ at the time of preparation (fresh samples)

Example	Composition	Appearance of System/Solution^	Stability of Pxt solution*	Compatability with Licaps Capsule*
40	Labrafac CM10.....9.0mL Pharmasolve.....1.0mL Tween 80.....2 drops Ascorbic acid.....1.0mg Propyl Gallate.....1.0mg Drug.....500mg	clear pale yellow solution	clear pale yellow solution	Yes
41	Labrasol.....9.0mL Pharmasolve.....1.0mL Tween 80.....2 drops Ascorbic acid.....1.0mg Propyl Gallate.....1.0mg Drug.....500mg	clear pale yellow solution	clear pale yellow solution	Yes
42	Cithrol 4DL.....9.0mL Pharmasolve.....1.0mL Tween 80.....2 drops Ascorbic acid.....1.0mg Propyl Gallate.....1.0mg	clear pale yellow solution	clear pale yellow/white solution	Yes

	Drug.....500mg			

* stored at RT for 10 days (visual observation), ^ at the time of preparation (fresh samples)

Example 43	Labrasol.....9.0mL Pharmasolve.....1.0mL Tween 80.....2 drops Ascorbic acid.....1.0mg Propyl Gallate.....1.0mg Sureteric.....32.0mg Drug.....500mg Capsule: Licaps size 1 (fill 20 capsules)

Example 44	Labrasol.....9.0mL Pharmasolve.....1.0mL Tween 80.....2 drops Ascorbic acid.....1.0mg Propyl Gallate.....1.0mg Eudragit L30D55.....42.0mg Drug.....500mg Capsule: size 11 oblonge softgel (fill 15 softgel capsules)

5

Example 45	Labrafac CM10.....9.0mL Pharmasolve.....1.0mL Tween 80.....2 drops Ascorbic acid.....1.0mg Propyl Gallate.....1.0mg Aquateric.....52.0mg Drug.....500mg Capsule: size 0 Hard Shell,Banded (fill 15 capsules)

CLAIMS

1. An oral swallow capsule containing paroxetine dissolved in a carrier.

2. An oral swallow capsule comprising a capsule shell containing paroxetine as the free base or a pharmaceutically acceptable salt or solvate thereof in solution in a liquid or solid carrier.

3. A capsule according to claim 2 in which the carrier is a liquid solvent present in the capsule as a flowable liquid, as a viscous liquid or semi-solid or as a gel.

4. A capsule according to claim 2 in which the carrier is a solid or semi-solid solvent.

5. A capsule according to claim 4 in which the solid or semi-solid solvent is selected from natural and synthetic fats and waxes, and film-forming and thermoplastic polymers.

6. An oral swallow solid dosage form containing paroxetine dissolved in a solid, semi-solid or gel carrier.

7. A solid dosage form comprising tablets, pellets, spheroids, granules, lozenges or gels in which paroxetine is present as a solid solution in a polymeric carrier.

8. Capsules and solid dosage forms according to any one of claims 1 to 7 which are coated to assist in administration of the active ingredient.

9. Capsules and solid dosage forms according to claim 8 which are coated with coatings to delay or control release of paroxetine and/or coatings for taste-masking.

10. Capsules and solid dosage forms according to any one of claims 1 to 9 in which paroxetine is used as the hydrochloride hemihydrate or anhydrate.

11. Capsules and solid dosage forms according to any one of claims 1 to 10 in which paroxetine is used as paroxetine hydrochloride in a form other than the hemihydrate, which is formulated under conditions such there is no detectable conversion to hemihydrate during the manufacturing process.

12. Capsules and solid dosage forms according to claim 11 in which the paroxetine hydrochloride is used in an amorphous form or as a crystalline anhydrate.

13. Capsules and solid dosage forms according to claim 12 in which the paroxetine hydrochloride is dissolved in a carrier which is essentially hydrophobic or anhydrous.

14. Capsules and solid dosage forms according to claim 12 or 13 in which the paroxetine hydrochloride is dissolved in a carrier in the presence of excipients, which are essentially hydrophobic or anhydrous.

15. A pharmaceutical formulation comprising a solution of paroxetine in a blend of a solubilising agent and a lipid and/or oil.

16. A process for preparing a formulation acording to claim 15 which comprises dissolving paroxetine in a solubilising agent and blending the resultant solution with a lipid and/or oil.

17. The use of paroxetine dissolved in a carrier to manufacture oral swallow capsules or solid dosage forms according to any one of claims 1 to 14 for the treatment or prophylaxis of one or more of the disorders;

18. A method of treating the disorders which comprises administering an effective or prophylactic amount of paroxetine as a solution in a carrier in an oral swallow capsule or solid dosage form according to any one of claims 1 to 14 to a mammal suffering from one or more of the disorders.

19. A method of treating the disorders which comprises administering an effective or prophylactic amount of paroxetine as a solution in a formulation according to claim 15 to a mammal suffering from one or more of the disorders.

INTERNATIONAL SEARCH REPORT

ational Application No.
PCT/GB 98/03471

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/445 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 31197 A (ABBOTT LAB) 10 October 1996 see page 8, line 35 - page 9, line 5 see claims 1-5	1-19
P,X	WO 98 31365 A (WARD NEAL ;JACEWICZ VICTOR WITOLD (GB); SMITHKLINE BEECHAM PLC (GB) 23 July 1998 see page 3, line 7-11; claim 9	1-7,10, 15-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 February 1999	10/02/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Herrera, S

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No.
PCT/GB 98/03471

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9631197 A	10-10-1996	CA 2216934 A	10-10-1996
		EP 0818990 A	21-01-1998
		US 5807574 A	15-09-1998
WO 9831365 A	23-07-1998	AU 5567398 A	07-08-1998

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 January 2001 (11.01.2001)

PCT

(10) International Publication Number
WO 01/02393 A1

(51) International Patent Classification[7]: C07D 405/12, C08B 37/00, A61K 31/445, 31/4525, A61P 25/00

(21) International Application Number: PCT/EP00/06121

(22) International Filing Date: 30 June 2000 (30.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI99A001459 1 July 1999 (01.07.1999) IT
MI99A002406 17 November 1999 (17.11.1999) IT

(71) Applicant *(for all designated States except US)*: **ITALFARMACO S.P.A.** [IT/IT]; Viale Fulvio Testi, 330, I-20128 Milano (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MASCAGNI, Paolo** [IT/IT]; Via Galli, 25, I-20058 Villasanta (IT). **BOTTONI, Giuseppe** [IT/IT]; Via Don Guanella, 5, I-24124 Bergamo (IT).

(74) Agent: **GERVASI, Gemma**; Notarbartolo & Gervasi S.p.A., Corso di Porta Vittoria, 9, I-20122 Milan (IT).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/02393 A1

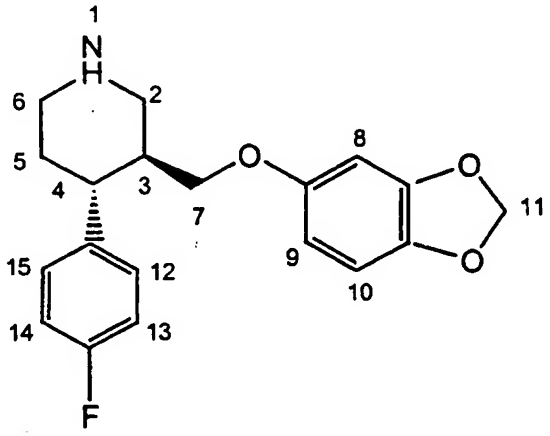
(54) Title: COMPLEXES OF PAROXETINE, WITH CYCLODEXTRINS OR CYCLODEXTRIN DERIVATIVES

(57) Abstract: Complexes of paroxetine, as free base or salt, with a cyclodextrin or a cyclodextrin derivative having a molar ratio between paroxetine and cyclodextrin ranging from 1:0.25 to 1:20, suitable for use in liquid and solid pharmaceutical compositions for oral and parenteral administration.

COMPLEXES OF PAROXETINE, WITH CYCLODEXTRINES OR CYCLODEXTRIN DERIVATIVES

Prior art

Paroxetine is an organic base having the following formula:



It is used as a therapeutic agent in several pathological forms and particularly in depression and Parkinson's disease because of its inhibitory activity on the neuronal recaptation of serotonin (5-HT).

In the pharmaceutical applications paroxetine is commonly used in its crystalline form of hemihydrated hydrochloride (U.S. 4,721,723). However, the poor solubility in water of this compound limits the possibility to prepare liquid pharmaceutical forms containing a suitable concentration of active principle while solid pharmaceutical forms show a limited bioavailability and a remarkable variability in plasmatic levels in different patients.

Paroxetine hydrochloride in an amorphous form, having the advantage of a faster solubilisation, is disclosed in patents EP810224, WO 98/31365, US 5.672.612 and WO 99/16440.

EP810224 and WO 98/31365 disclose a preparation procedure but they do not point out the particular advantages of it, except the faster solubilisation due to the amorphous state of the product.

In US 5.672.612 it is claimed that paroxetine in an amorphous form is stable if present in the composition with ethanol at a % by weight of up to 10% and preferably of about 1-4%. However, such a content of ethanol is not commonly

acceptable and desirable in a pharmaceutical composition.

In WO 99/16440 other compositions containing paroxetine hydrochloride are described, starting from the same preparation of paroxetine HCl in ethanol, wherein a variety of compounds such as acids, hydroxyacids and polyhydroxylated substances might allow to obtain the same stabilising effect. In the Patent Application it is claimed that all the above compounds should have the same effect. Among the compositions described, a composition comprising a cyclodextrin and in particular hydroxypropyl-β-cyclodextrin is cited and claimed. However, the complex and its characteristics are not described. Furthermore, the problem relating to the presence of ethanol in the formulation remain unaltered. In fact said compositions are prepared by processes comprising:

dissolution of paroxetine base in absolute ethanol;

preparation of a hydrochloric acid solution in absolute ethanol;

addition of the hydrochloric acid solution in absolute ethanol to the solution of paroxetine base;

stirring in order to obtain a composition of paroxetine hydrochloride in ethanol;

adding of a polyhydroxylated compound, if any; and

drying of the above mentioned composition.

Since said processes operate in ethanol, they necessarily bring to a final product containing significant amounts of this solvent and this results in obvious drawbacks from the pharmaceutical point of view.

The use of ethanol is also not convenient from the point of view of the process.

Paroxetine salts, due to their ionic characteristics, are not directly absorbed by the gastrointestinal wall but they must first transform in the non salified paroxetine which, being lipophylic, is able to go through the gastrointestinal mucosa.

The transformation process is linked to the equilibrium constant represented by the formula: paroxetine HX $\rightleftharpoons$ paroxetine + HX and it is influenced by the pH of the medium.

On the other hand, paroxetine as free base is unsuitable to be used as such for the manufacturing of pharmaceutical forms as it consists of a dense liquid having oily characteristics or of a waxy solid. Moreover, it easily decomposes becoming oxidized and its solubility in water is very low.

Actually, in Patent Application WO99/26625 capsules containing paroxetine as free base or as a pharmaceutically acceptable salt in a liquid or solid carrier are claimed.

However, the several reported compositions (Examples 1-30) all refer to the use of paroxetine hydrochloride, while the subsequent Examples (Examples 31-44) refer to paroxetine liquid formulations (it is not specified if as free base or as salt) in Pharmasolve, oil and lipids.

As solid or semisolid carriers fats, waxes and filmogenic or thermoplastic polymers are cited.

Summary of the invention

We have now found that the problems of the prior art can be solved by complexes of paroxetine, as free base or as salt, with a cyclodextrin or a cyclodextrin derivative.

The complexes according to the present invention may have the form of a flowing powder, they show a high chemical stability, an improved solubility in water and are suitable for the preparation of liquid or solid pharmaceutical compositions. Furthermore, paroxetine present in said complexes shows a pH-independent dissolution behaviour.

Said complexes may be prepared by a process comprising the following steps:

paroxetine, as free base or as salt, a cyclodextrin or a cyclodextrin derivative and water are mixed;

the obtained mixture is stirred in order to obtain an homogeneous solution or dispersion and stirring is continued until formation of a complex;

the solid is filtered and then dried or the solution or dispersion is dried and the solid recovered.

Brief description of the figures

Fig. 1 shows the solubility of complexed paroxetine HCl at different molar ratios between β-cyclodextrin and paroxetine HCl.

Fig. 2 shows the thermogram obtained in a DSC test carried out on a complex between paroxetine HCl and β-cyclodextrin 1 hour after preparation.

Fig. 3 shows the thermogram obtained in a DSC test carried out on a complex between paroxetine HCl and β-cyclodextrin 7 days after preparation.

Fig. 4 shows the thermogram obtained in a DSC test carried out on a complex between paroxetine HCl and β-cyclodextrin 3 months after preparation.

Fig. 5 shows the thermogram obtained in a DSC test carried out on a complex between paroxetine acetate and β-cyclodextrin two weeks after preparation.

Fig. 6 shows the thermogram obtained in a DSC test carried out on a complex between paroxetine HCl and 2-hydroxypropyl-β-cyclodextrin two weeks after preparation.

Fig. 7 shows the thermogram obtained in a DSC test carried out on a complex between paroxetine base and β-cyclodextrin two weeks after preparation.

Fig. 8 shows a X-ray spectrum of a complex between paroxetine HCl and β-cyclodextrin, wherein the complex has been prepared according to Example 1.

Fig. 9 shows a X-ray spectrum of a complex between paroxetine HCl and β-cyclodextrin, wherein the complex has been prepared according to Example 6.

Fig. 10 shows the thermogram obtained in a DSC test carried out on a complex between paroxetine HCl and β-cyclodextrin immediately after compression in an infrared press.

Fig. 11 shows the thermogram obtained in a DSC test carried out on a complex between paroxetine HCl and β-cyclodextrin three days after compression in an infrared press.

Detailed description of the invention

The present invention refers to complexes of inclusion of paroxetine, as free base or as salt, with a cyclodextrin or a derivative thereof.

Said complexes are preferably prepared according to a process characterised by the following steps:

(a) paroxetine, as free base or as salt, a cyclodextrin or a cyclodextrin derivative and water are mixed;

(b) the obtained mixture is stirred in order to obtain an homogeneous solution or dispersion and stirring is continued until formation of the complex; and

(c) the water is partially removed in order to obtain a solid complex with a desired water content.

Preferably, the complexes of the invention have a water content between 1 and 20%, preferably between 2 and 15%, by weight.

Paroxetine may be used as a free base or as a salt with an organic or an inorganic acid.

Preferably said organic or inorganic acid is selected from the group comprising acetic acid, maleic acid, hydrochloric acid and methanesulfonic acid. Among these, hydrochloric acid is particularly preferred.

Paroxetine base may be used either as a waxy solid or as a oily liquid.

Preferably, said cyclodextrin is a α-, β-, or γ-cyclodextrin, in anhydrous or hydrated form.

Said cyclodextrin derivative is preferably selected from the group consisting of eptakis (2-6-di-O-methyl)-β-cyclodextrin, (2,3,6-tri-O-methyl)-β-cyclodextrin, monosuccinyl eptakis (2,6-di-O-methyl)-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, sulphated cyclodextrin or cyclodextrin containing aminoalkyl groups.

Preferably, in the present invention β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin are used.

Preferably, in step a) 1 to 100 g of cyclodextrin or cyclodextrin derivative are used per litre of water.

Preferably, paroxetine as free base or as salt are used in such a quantity as to obtain complexes with a molar ratio between paroxetine and cyclodextrin ranging from 1:0.25 to 1:20 and preferably from 1:0.5 to 1:2.

Slightly different operative patterns may be used when preparing complexes of paroxetine base and of a paroxetine salt.

In detail, when preparing a complex with paroxetine base, step a) is preferably carried out according to the following steps:

a_1) a cyclodextrin or a cyclodextrin derivative is added to water;

a_2) the solution or dispersion of step a_1) is kept under stirring for a time from 30 to 180 minutes at a temperature between 25°C and 50°C; and

a_3) paroxetine base is dispersed in the solution or dispersion of step a_2).

When preparing a complex with a paroxetine salt, step a) is preferably carried out according to the following steps:

a_1) paroxetine base is salified with an organic or inorganic acid; and

a_2) a cyclodextrin or a cyclodextrin derivative is added under stirring to the salified paroxetine.

The salification of paroxetine base can be carried out using different procedures. For example, paroxetine base may be dispersed in water under stirring and an aqueous solution of the selected acid may be added to the dispersion until formation of a solution. Alternatively, paroxetine base may be added to an aqueous solution of the selected acid.

When preparing both types of complexes, step b) is preferably carried out by mechanical stirring or by ultrasounds. Preferably, in order to allow formation of the complex, stirring is carried out at a temperature 25° and 50 °C for a time up to 48 hours, preferably between 3 and 24 hours.

Step c) is usually carried out by freeze drying, vacuum drying or drying under an inert gas flux. Preferably, vacuum drying is carried out at a temperature from 20 to 40 °C and drying under an inert gas flux at a temperature from 5 to 40 °C.

Preferably, when preparing a complex of paroxetin base, step c) can also be carried out according to the following steps:

c_1) the dispersion of step c) is cooled and maintained at a temperature between 4°C and 20°C for 1 to 20 hours;

c_2) the precipitate obtained in step c_1) is recovered by filtration; and

c_3) the solid product recovered in step c_2) is dried under vacuum or under an inert gas flux until the desired water content is reached.

As will be described in detail in the Examples below, different drying procedures lead to complexes having different characteristics: complexes in an amorphous state are obtained by freeze drying, while crystalline complexes are obtained by vacuum drying.

As an alternative to the above disclosed process, complexes containing paroxetine base may be prepared by slowly adding to a cyclodextrin or a derivative thereof paroxetine in the form of an oily liquid in a mixer for powders kept under stirring for a time from 3 to 24 hours, at a temperature from 25 to 50 °C.

Also in this case the treatment in the mixer for powders may be substituted with an ultrasonic treatment.

As a further alternative, complexes containing paroxetine base can be prepared by formation of a slurry consisting of a cyclodextrin or a derivative thereof, paroxetine base and water, wherein the amount of the latter compound ranges from 20 to

100% of the weight of the solid substances. The slurry is then mixed and dried as described above.

The product obtained through any of the above processes is then usually sieved on a 250 μm sieve in order to obtain a product with a particle size distribution suitable for further processing.

The complexes of the present invention are new products as proved by the results of the characterisations reported below.

In particular these products have the following characteristics:

- the form of a flowing powder, a suitable physical state for the production of pharmaceutical forms;
- a higher solubility in water with respect to the non-complexed product which may give a decreased variability in plasmatic levels;
- a greater stability in comparison with the non-complexed product;
- by NMR characterization they show a positive variation of the chemical shift of many protons of paroxetine and a negative variation of the protons of cyclodextrin present in its cavity;
- by differential thermal analysis (DSC) the complexes with paroxetine base show absence of the decomposition peak of paroxetine base between 260° and 300°C while the complexes with a paroxetine salt show absence of thermal events at temperatures corresponding to the peak of fusion of the relative non-complexed salt.

Furthermore, thanks to the process used the products of the present invention are free from organic solvents, such as ethanol, which are present in many preparations of the known technique.

Thanks to their characteristics, the products of the present invention may be used for the preparation of solid and liquid pharmaceutical compositions for oral and parenteral administration with improved effects in the treatment of depression and Parkinson's disease and other pathologies curable by administration of paroxetine. Said compositions comprise a pharmaceutically effective dose of a complex according to the present invention in mixture with pharmaceutically acceptable diluents or excipients.

The present invention also refers a therapeutic method for the treatment of

subjects suffering from depression or Parkinson's disease, and from any other pathology curable with paroxetine, consisting in the administration of said complexes in an amount corresponding to 5-40 mg per day of paroxetine orally and corresponding to 1-20 mg per day of paroxetine parenterally.

The present invention may be further understood with reference to the following Examples.

EXAMPLE 1

1 g of paroxetine base is dispersed in 150 g of deionized water under stirring. A solution of 0.11 g of HCl in 28 g of water is added to the dispersion under stirring and stirring is continued until paroxetine is completely solubilised.

The pH of the solution is about 6.

3.5 g of β-cyclodextrin in powder are added to the solution and the obtained dispersion is heated to 40 °C under nitrogen flux and with vigorous stirring for 3 hours.

An opalescent solution is obtained containing a little amount of undissolved residue which is removed by filtration through a cellulose acetate filter having 0.45 μm porosity.

The obtained solution is freeze-dried and 4.3 g of a product with a molar ratio between paroxetine HCl and β-cyclodextrin of 1:1 and with a water content of 5.4% by weight are obtained.

The product has been characterised as described below.

EXAMPLES 2-5

These Examples have been carried out according to the method described in Example 1 using amounts of reacting substances such as to obtain final products with the following molar ratios between β-cyclodextrin and paroxetine HCl:

Table1

Example N.	Molar Ratio
2	0.25:1
3	0.50:1
4	2.0:1
5	3.0:1

The products obtained from these examples and from Example 1 have all been characterised for their solubility in water compared to non-complexed paroxetine HCl, as described below.

EXAMPLE 6

1 g of paroxetine base is suspended in a solution consisting of 25 g of deionized water and 2.8 ml of 1 N HCl and, under vigorous stirring, 3.5 g of β-cyclodextrin in powder are added.

The mixture is kept under stirring for 24 hours at 25 °C under nitrogen flux.

The obtained mixture is partially concentrated and finally vacuum dried at 25 °C for 48 hours.

4.4 g of a product with a molar ratio between paroxetine HCl and β-cyclodextrin of 1:1 and with a water content of 5.4% are obtained.

EXAMPLE 7

Example 1 has been repeated with the difference that acetic acid (110 mg) instead of hydrochloric acid has been used. 4.3 g of the relative complex have been obtained.

EXAMPLE 8

Example 1 has been repeated with the difference that 2-hydroxypropyl-β-cyclodextrin (4.0 g) instead of β-cyclodextrin has been used.

4.7 g of the relative complex have been obtained.

The products of the Examples 7 and 8 have been characterised as described for the product of Example 1 with similar results.

EXAMPLE 9

In a glass reactor 3.5 g of β-cyclodextrin are solubilised in 50 ml of deionized water at 45 °C.

1 g of paroxetine base is dispersed in the obtained solution and the suspension is kept under stirring at 45 °C for a 5 hours.

The obtained suspension is cooled to 15 °C and a precipitate is recovered by filtration on a cellulose acetate filter.

The obtained product is dried in a stove under vacuum at 40 °C for 12 hours, to a 9% residual content of water, determined by the Karl Fisher method.

4.3 g of product in the form of a flowing powder are obtained wherein the molar

ratio between basic paroxetine and β-cyclodextrin is about 1:1.3, as determined by spectrophotometry at 293 nm in comparison with a standard solution of paroxetine base.

The product has been sieved through a 250 μm sieve and characterised as described below.

EXAMPLE 10

In a mixer for powders 20 g paroxetine base in form of oil are slowly added under stirring to 70 g of β-cyclodextrin.

The stirring is continued for 12 hours obtaining an homogeneous mixture.

86 g of product in the form of a flowing powder are obtained which are sieved through a 250 μm sieve.

The product has a molar ratio between basic paroxetine and β-cyclodextrin of about 1:1.

The product has been characterised as described later for the product of Example 9 with similar results.

EXAMPLE 11

Example 9 has been repeated with the difference that 2-hydroxypropyl-β-cyclodextrin (4.0 g) has been used instead of β-cyclodextrin.

4.7 g of product in form of a flowing powder have been obtained.

Also this product has been characterised as described for the product of Example 9 with similar results.

EXAMPLE 12

Characterisation of the complexes of the invention

A) Solubility

The solubility of the products obtained in Examples 1-5 and 9 has been evaluated in comparison with that of the non-complexed paroxetine base or paroxetine HCl

i) Complexes of Example 1-5

A solubility test was carried out on an amount of the complexes of Examples 1 to 5 corresponding 500 mg of paroxetine HCl and, as a comparison, on 500 mg of non-complexed paroxetine HCl.

Each sample was introduced into a container containing 5 ml of deionized water. The containers, closed with a plug were then set under stirring in a thermostatic

bath at 25°C for 24 hours.

The obtained suspensions were then filtered through a cellulose acetate filter and analysed by spectrophotometry at 295 nm, in comparison with a standard solution of paroxetine.

The results obtained are reported in Fig. 1 wherein the solubility of paroxetine HCl (in mg/ml) is represented as a function of the molar ratio between β-cyclodextrin and paroxetine HCl.

From the plot one may note that while the solubility of the non-complexed paroxetine HCl is 5 mg/ml, as reported in literature, the solubility of the complexes is higher and increases with the increase of the molar ratio between β-cyclodextrin and paroxetine HCl, reaching a solubility up to 45 mg/ml at a 1:1 ratio.

ii) Complex of Example 9

5 g of the product of Example 9 were added to 10 ml of deionised water and kept under stirring for 4 hours at room temperature.

The suspension was then filtered through a cellulose acetate filter in order to remove the undissolved product.

The solution was analysed by 293 nm spectrophotometry against a standard solution of paroxetine base.

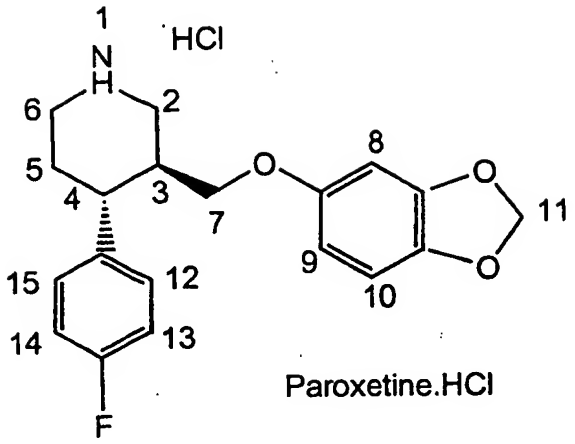
The content of paroxetine base in the solution was 2.3 mg/ml. As a comparison, the solubility of the non-complexed paroxetine base was also measured. A solubility of 0.3 mg/ml was found.

B) <u>NMR characterisation</u>

This characterisation has been carried out on the products of Example 1 and 9 in comparison with Paroxetine and Paroxetine HCl, by 1HNMR 200 MHz in D_2O.

The results are reported in Table 2 and 3 wherein one may notice the chemical shift positive variation of many protons of paroxetine and the chemical shift negative variation of the proton of β-cyclodextrin inside its cavity.

This proves that the product consists of a complex of paroxetine base or salt with β-cyclodextrin.



Paroxetine.HCl

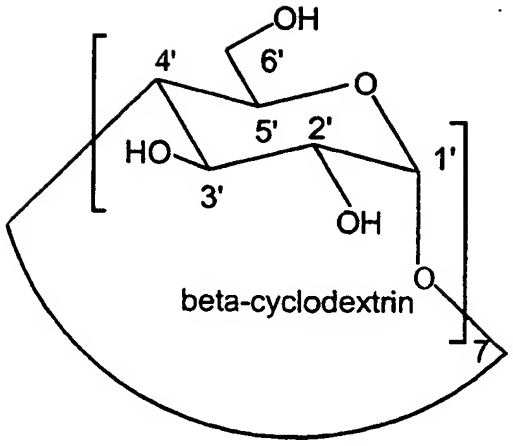


Table 2

Protons	multiplicity	Paroxetine HCl	Paroxetine base	Product of Example 1	Product of Example 9
$H_{12, 15}$	dd(2H)	7.18 (-0.01)	7.18 (-0.01)	7.25 (0.06)	7.25 (0.06)
$H_{13, 14}$	t (2H)	6.97 (-0.02)	6.97 (-0.02)	7.09 (0.10)	7.09 (0.10)
H_{10}	d (1H)	6.60 (-0.02)	6.60 (-0.02)	6.64 (0.02)	6.64 (0.02)
H_8	d (1H)	6.32 (-0.01)	6.32 (-0.01)	6.47 (0.14)	6.47 (0.14)
H_9	dd (1H)	6.11 (-0.02)	6.11 (-0.02)	6.09 (-0.04)	6.09 (-0.04)
H_{11}	s (2H)	5.79 (-0.02)	5.79 (-0.02)	5.86 (1H) (0.05)	5.86 (1H) (0.05)
				5.80 (1H) (-0.01)	5.80 (1H) (-0.01)
H4	t (1H)	3.08 (----)		3.20 (0.12)	
H6a	dt (1H)	2.85 (-0.02)		2.98 (0.11)	
H3	m (1H)	2.34 (----)		2.44 (0.10)	

Table 3

Proton	Multiplicity	β-cyclodextrin	Product of Example 1	Product of Example 9
$H_{3'}$	t (1H)	3.94	3.81 (-0.13)	3.81 (-0.13)
$H_{2'}$	dd (1H)	3.62	3.63 (0.01)	3.63 (0.01)
			3.64 (0.02)	3.64 (0.02)

C) Differential thermal analysis (DSC)

DSC tests have been carried out on the products prepared in Example 1, 7, 8 and 9, using the following conditions:

Equipment: Perkin Elmer DSC7

Temperature Range: 50-300 °C (Examples 1 and 9)
50-200 °C (Examples 7 and 8)

Heating Rate: 10 °C/minute

i) Complex of Example 1

A DSC test was first carried out on the product prepared in Example 1 one hour after preparation. The obtained thermogram is reported in Figure 2 and it is characterised by the absence of thermal events in the 100-200 °C range while it shows a peak between 230 and 250 °C.

Considering that the commonly used paroxetine HCl (hemihydrated form) has a melting point equal to 143.5 °C and that the other known forms of paroxetine HCl have melting points ranging from 117 to 164 °C, one may conclude that the product of the Example 1 is a new product.

The DSC analysis was then repeated on the same product after storing at 25 °C and 60% relative humidity for 7 days (Fig. 3) and 3 months (Fig. 4), respectively.

The thermograms show that the product is stable in time and it is not transformed into known crystalline forms of paroxetine HCl.

ii) Complex of Example 7

A DSC test was carried out on the complex of Example 7 two weeks after preparation. The thermogram (Fig.5) shows absence of thermal events at temperatures below 200°C.

iii) Complex of Example 8

A DSC test was carried out on the complex of Example 8 two weeks after preparation. The thermogram (Fig. 6) shows absence of thermal events at temperatures below 200°C.

iv) Complex of Example 9

A DSC test was carried out on the complex of Example 9 two weeks after preparation.

The thermogram is reported in the Fig.7. One may notice the absence of the decomposition peak between 260 °C and 300 °C characteristic of paroxetine base, as a demonstration of the occurred complexation.

D) X-ray diffraction

Samples of 200 mg of the products obtained in Example 1 and in Example 6 have been analysed by X-ray diffraction using a PW 3710 difractometer (Philips Analytical X-Ray B.V.)

The obtained spectra show that different drying procedures lead to complexes having different characteristics. In fact, while an amorphous complex containing paroxetine HCl is obtained in Example 1 by freeze drying (Fig 8), a crystalline complex containing paroxetine HCl is obtained in Example 6 by vacuum drying (Fig. 9).

E) Stability evaluation

i) Compression behaviour

About 50 mg of the product obtained as described in Example 1 were compressed in an infrared press at a pressure of 10 T for 5 minutes.

Figure 10 shows the thermogram (DSC) carried out immediately after compression and Figure 11 shows the thermogram carried out 3 days from compression, after storing at room temperature.

Also this test confirms the stability of the product which is not transformed by pressure to known forms of paroxetine HCl.

ii) Chemical stability

The product of Example 1 has been tested using accelerated stability tests.

Samples of the product as a solid or in solution (at a concentration of 4 mg/ml of paroxetine HCl) were stored for one month at 40°C. As a reference, at the same

time equivalent samples were stored at 4°C.

Quantitative determination of paroxetine HCl was carried out by HPLC.

The results obtained show that the drug does not undergo any alteration in the above reported conditions.

iii) Stability at 60°C

About 200 mg of paroxetine base and 1 g of the complex of Example 9 (corresponding to about 180 mg of paroxetine base) have each been introduced in a neutral white glass containers and stored, opened, in an oven at 60 °C.

The product in the two containers has been visually examined after 48 hours of storage.

The results are reported in the following table:

Table 4

	Paroxetine base	Paroxetine base-β-cyclodextrin
Initial	Straw-Yellow liquid	White powder
48 h 60 °C	Brown liquid	White powder

The results obtained show that the incorporation of paroxetine base into β-cyclodextrin stabilises the active principle.

F) IGROSCOPICITY

The water content of the product of Example 1 before and after the treatment described below has been determined using the Karl Fisher method.

The product of Example 1 was sieved through a 600 μm sieve in order to obtain an homogeneous powder and weighed exactly in an open glass crucible.

The crucible was put in a climatic chamber at 25°C with 60% relative humidity for 2 or 7 days and then weighed again. The percentage of water absorbed was estimated by weight difference with respect to the initial weight. The results obtained are reported in Table 5.

Table 5

Time	Water content (% by weight)
0	5.4
2 days	10.5
7 days	11

EXAMPLE 13

Tablets having the following composition:

Product of Example 6 98 mg
Calcium Phosphate 259 mg
Sodium Starch Glycolate 2 mg
Magnesium Stearate 3 mg

were prepared by direct compression using a rotary press with a 9 mm punch.

A taste masking coating and a gastro-enteric coating were achieved by applying respectively 2 mg/cm^2 of a blend of methacrylic acid copolymer/ Sodium Carboxymethylcellulose and 1.5 mg/cm^2 of a methacrylic acid copolymer.

A dissolution test was performed on the tablets described above and on commercially available tables of non-complexed paroxetine HCl hemihydrate, all containing the same amount of active principle.

The test was carried out according to European Pharmacopeia, 3rd Ed. 1997, 2.9.3 page 128, using the following conditions:

Apparatus: Paddle
Medium: HCl 0.1 N or Phosphate Buffer pH 6.8
Stirring speed: 60 rpm
Temperature: 37°C

The percentage of paroxetine HCl dissolved was evaluated at 5, 15, 30 and 60 minutes by UV detection at 294 nm, using paroxetine HCl as a standard.

The results obtained in HCl 0.1 N are reported in Table 6 while the results obtained in Phosphate Buffer are reported in Table 7. The values indicated are the average values obtained from three determinations.

Table 6

Time	Taste masked tablets	Gastro-enteric coated tablets	Commercially available tablets
0	0	0	0
5	25.4	0	31.6
15	64.7	0.3	68.4
30	89.9	1.2	93.7
60	100	2.5	100

Table 7

Time	Taste masked tablets	Gastro-enteric coated tablets	Commercially available tablets
0	0	0	0
5	30.6	33.9	17.1
15	64.5	64.9	29.3
30	75.9	81.9	42
60	82.8	87.5	58.1

The results obtained demonstrate that the solubility of the complex of paroxetine HCL-β-cyclodextrin is independent from the pH of the medium when formulated as taste masked tablets. Furthermore, when the complex is formulated as a gastro-protected tablet it shows a suitable dissolution behaviour in intestinal environment.

EXAMPLE 14

A formulation in drops comprising the product of Example 6 was prepared, having the following composition:

Product of Example 6	98 mg
Sucrose	100 mg
Flavour	50 mg
Depurated water to	1 ml.

The formulation has a concentration of paroxetine-HCl-β-cyclodextrin of 20 mg/ml and it is stable for up to 1 month of storage at 40°C.

CLAIMS

1. Complexes of paroxetine, as free base or as salt, with a cyclodextrin or with a cyclodextrin derivative.

2. Complexes as claimed in claim 1 characterised by the form of a flowing powder, chemical stability, absence of organic solvents, high solubility in water and DSC profile different from that of the corresponding non-complexed paroxetine or paroxetine salt.

3. Complexes as claimed in claim 2 characterised by the absence of ethanol.

4. Complexes as claimed in claim 1 characterised in that they have a water content of between 1 and 20% by weight.

5. Complexes as claimed in claim 4 characterised in that said water content is between 2 and 15% by weight.

6. Complexes as claimed in claim 1, characterised in that said cyclodextrin is selected from the group consisting of α, β and γ-cyclodextrin.

7. Complexes as claimed in claim 6, characterised in that said cyclodextrin is a β-cyclodextrin.

8. Complexes as claimed in claim 1, characterised in that said cyclodextrin derivative is selected from the group consisting of eptakis (2,6-di-O-methyl)-β-cyclodextrin, eptakis (2,3,6-tri-O-methyl)-β-cyclodextrin, monosuccinyl-eptakis(2,6-di-O-methyl)-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, sulphated cyclodextrin and cyclodextrin containing aminoalkyl groups.

9. Complexes as claimed in claim 8, characterised in that said cyclodextrin derivative is the 2-hydroxypropyl-β-cyclodextrin.

10. Complexes as claimed in claim 1, characterised in that said salt of paroxetine is a salt with an organic or inorganic acid.

11. Complexes as claimed in claim 10, characterised in that said organic or inorganic acid is selected from the group consisting of acetic acid, maleic acid, hydrochloric acid and methanesulfonic acid.

12. Complexes as claimed in claim 11 characterised in that said acid is hydrochloric acid.

13. Complexes as claimed in claim 1, characterised in that the molar ratio between paroxetine and said cyclodextrin or cyclodextrin derivative ranges from 1:0.25 to

1:20.

14. Complexes as claimed in claim 13, characterised in that the molar ratio between paroxetine and said cyclodextrin or cyclodextrin derivative ranges from 1:0.5 to 1:2.

15. Process for the preparation of the complexes as defined in claim 1, comprising the following steps:

(a) paroxetine, as free base or as salt, a cyclodextrin or a cyclodextrin derivative and water are mixed;

(b) the obtained mixture is stirred in order to obtain an homogeneous solution or dispersion and stirring is continued until formation of the complex; and

(c) the water is partially removed in order to obtain a solid complex with the desired water content.

16. Process as claimed in claim 15 characterised in that paroxetine is used as a free base.

17. Process as claimed in claim 15 characterised in that paroxetine is used as a salt.

18. Process as claimed in claim 15 characterised in that step b) is carried out by mechanical stirring or by ultrasounds.

19. Process as claimed in claim 15 characterised in that step c) is carried out by freeze drying, drying under vacuum or under an inert gas flux.

20. Process as claimed in claim 15 characterised in that in step c) a solid complex with a water content of between 1 and 20% by weight is obtained.

21. Process as claimed in claim 20 characterised in that said water content is between 2 and 15% by weight.

22. Process as claimed in claim 16 characterised in that step a) is carried out according to the following steps:

a_1) a cyclodextrin or a cyclodextrin derivative is added to water;

a_2) the solution or dispersion of step a_1) is kept under stirring for a time from 30 to 180 minutes at a temperature between 25° and 50°C; and

a_3) paroxetine base is dispersed in the solution or dispersion of step a_2).

23. Process as claimed in claim 17, characterised in that said step a) is carried out according to the following steps:

a_1) paroxetine base is salified with an organic or inorganic acid; and

a_2) a cyclodextrin or a cyclodextrin derivative is added under stirring to the salified paroxetine.

24. Process as claimed in claim 16 characterised in that step c) is carried out according to the following steps:

c_1) the dispersion of step b) is cooled and maintained at a temperature between 4°C and 20°C for 1 to 20 hours;

c_2) the precipitate obtained in step c_1) is recovered by filtration; and

c_3) the solid product recovered in step c_2) is dried under vacuum or under an inert gas flux until the desired water content is reached.

25. Process for the preparation of complexes as claimed in claim 1 comprising slowly adding paroxetine base in the form of an oily liquid to a cyclodextrin or to a cyclodextrin derivative in a mixer for powders or in an ultrasonic mixer and continuing the stirring for a time ranging from 3 to 24 hours at a temperature from 25 to 50 °C.

26. Pharmaceutical compositions containing as an active substance a pharmaceutically effective dose of a complex as defined in claim 1, in mixture with pharmaceutically acceptable diluents or excipients.

27. Pharmaceutical compositions as claimed in claim 26 in solid or liquid form, for oral and for parenteral administration.

28. Therapeutical method for the treatment of patients suffering from depression or Parkinson's disease or other pathologies curable with paroxetine consisting of the administration of a complex as defined in claim 1, in an amount corresponding to 5-40 mg per day of paroxetine by oral way and corresponding to 1-20 mg per day of paroxetine parenterally.

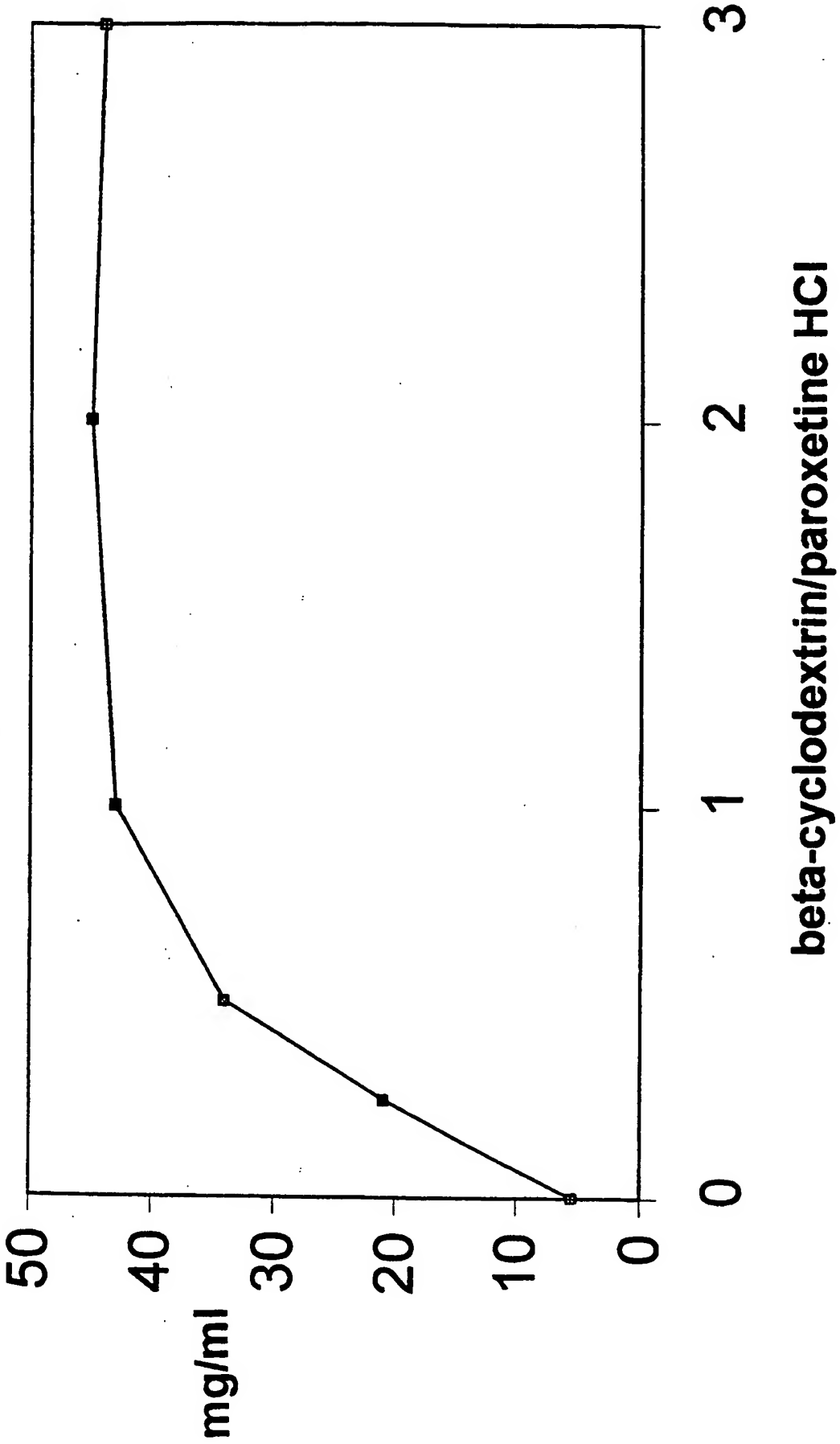


FIG. 1

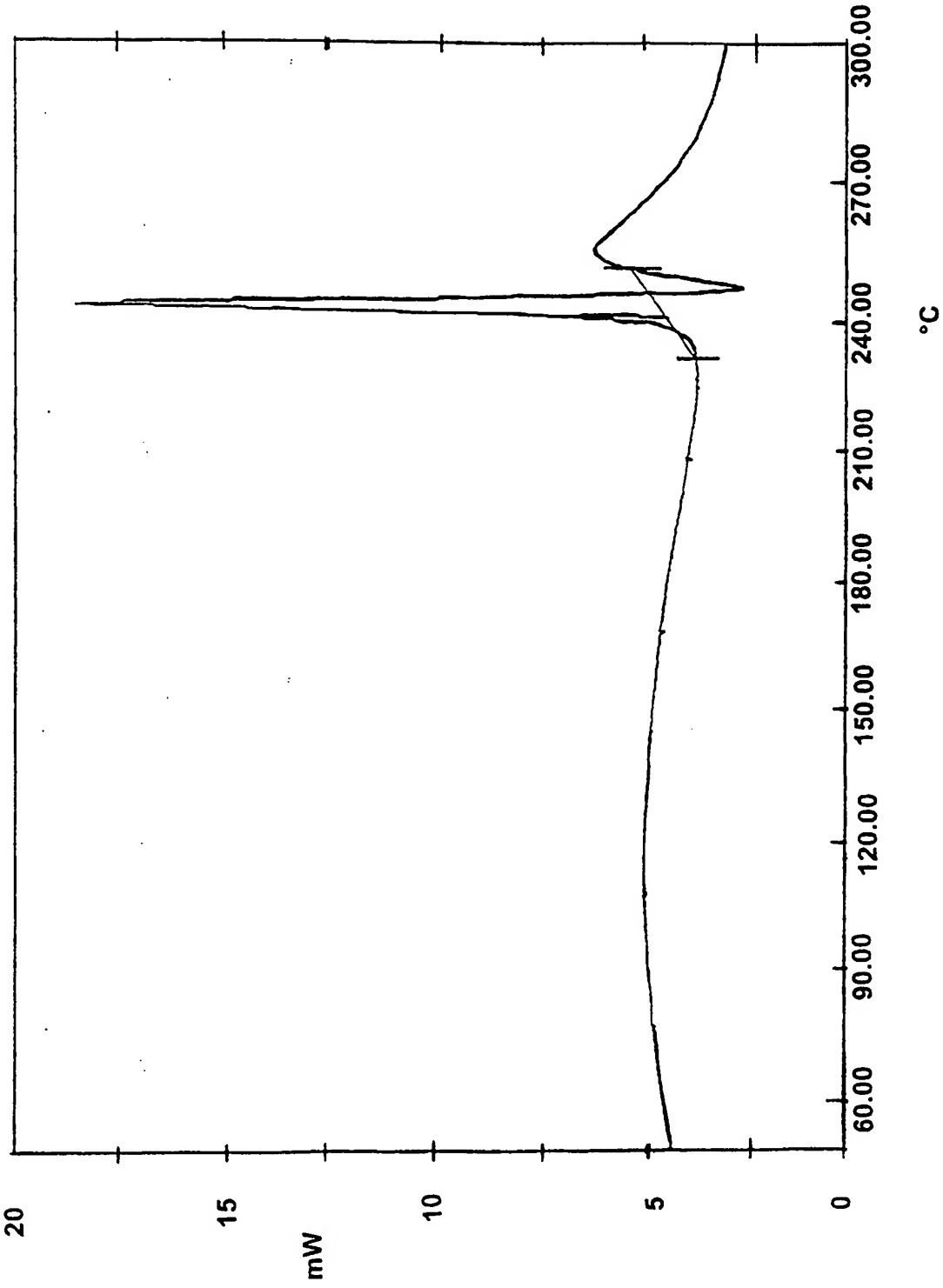

20
15
10
5
0
mW
60.00
90.00
120.00
150.00
180.00
210.00
240.00
270.00
300.00
°C

FIG. 2

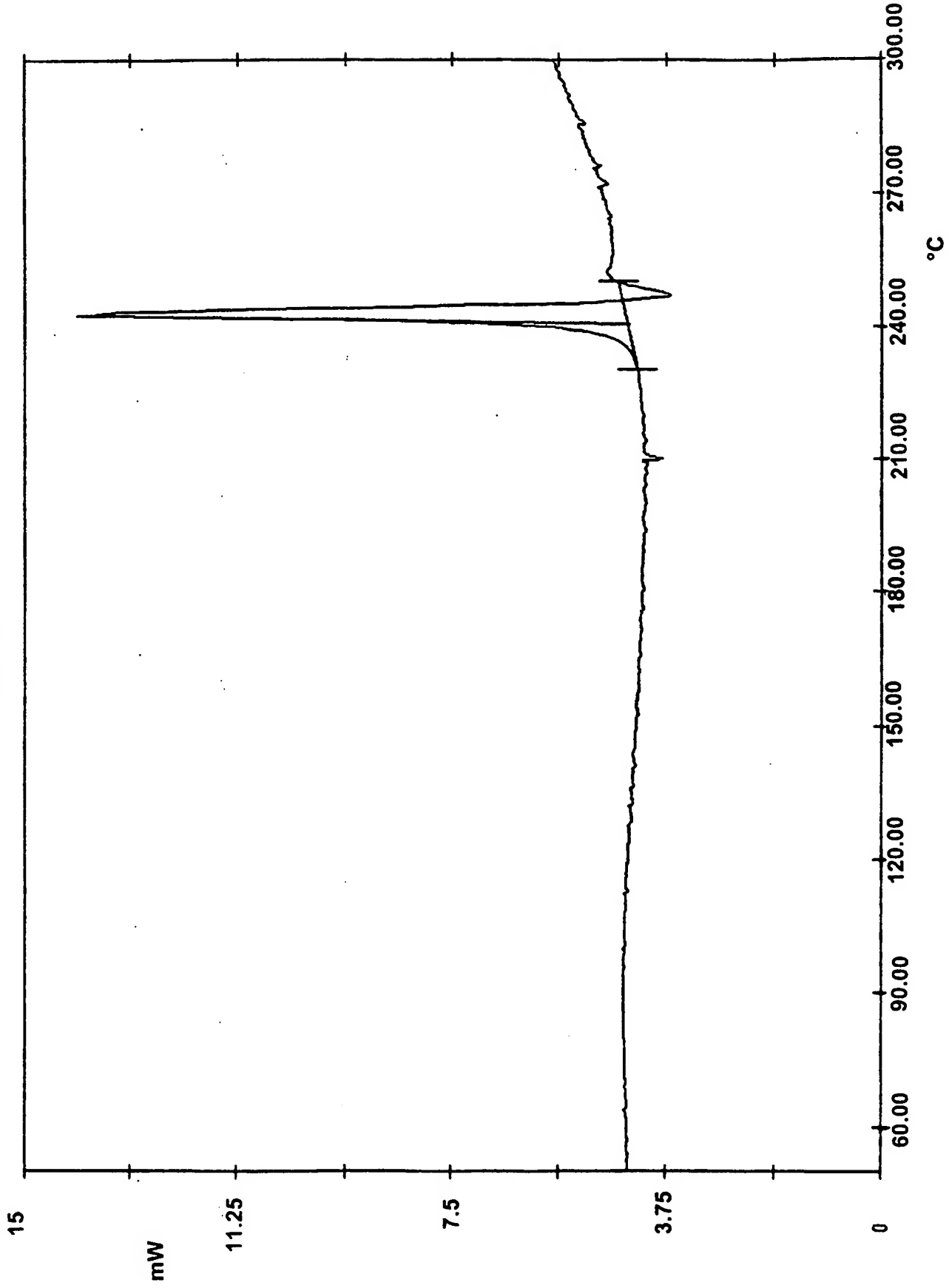

300.00
270.00
240.00
210.00
180.00
150.00
120.00
90.00
60.00
°C
15
11.25
7.5
3.75
0
mW

FIG. 3

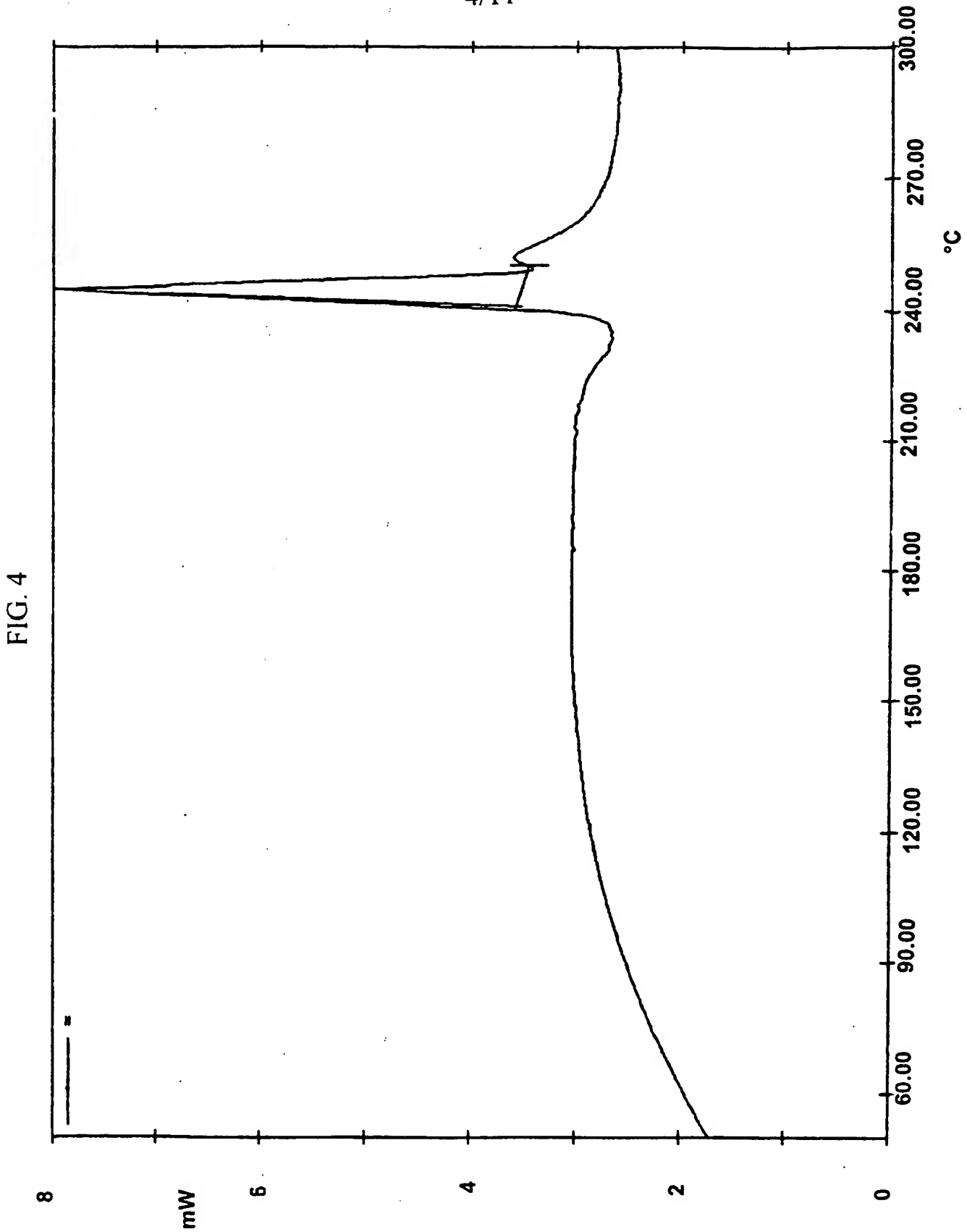
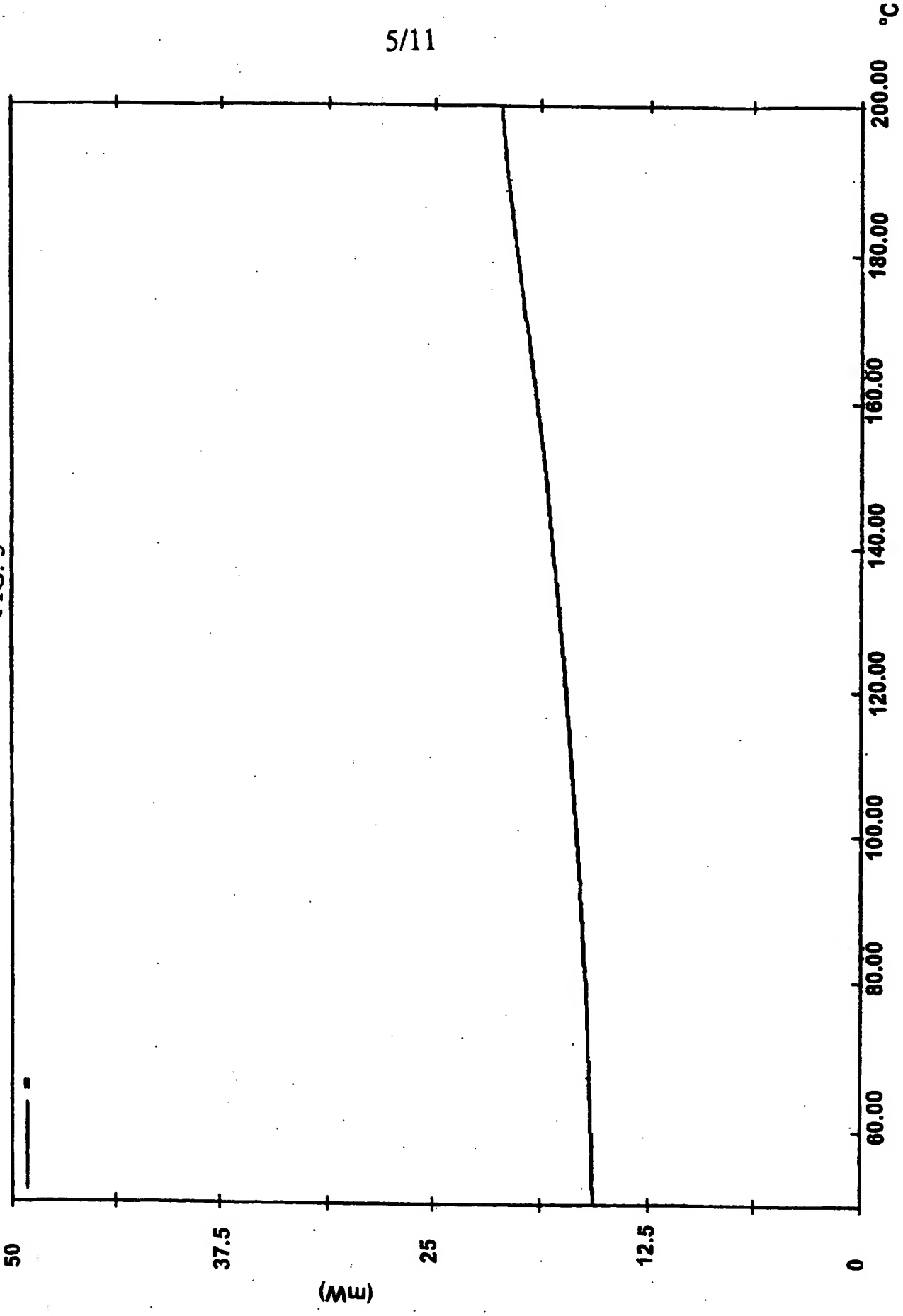

8
mW
6
4
2
0
60.00
90.00
120.00
150.00
180.00
210.00
240.00
270.00
300.00
°C

FIG. 4

FIG. 5


°C
200.00
180.00
160.00
140.00
120.00
100.00
80.00
60.00
50
37.5
25
12.5
0
(mw)

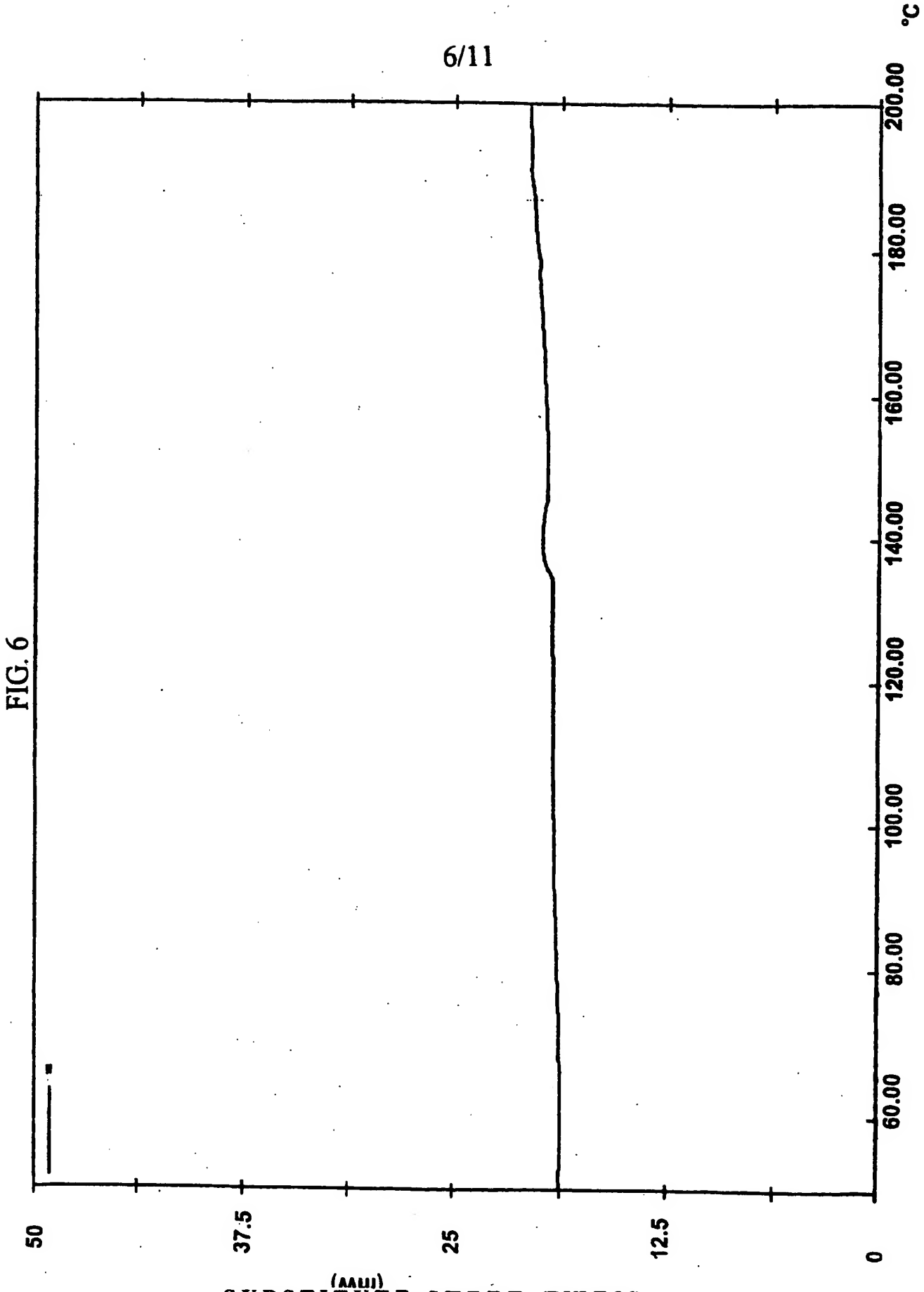

°C
200.00
180.00
160.00
140.00
120.00
100.00
80.00
60.00
50
37.5
25
12.5
0
(AAUI)

FIG. 6

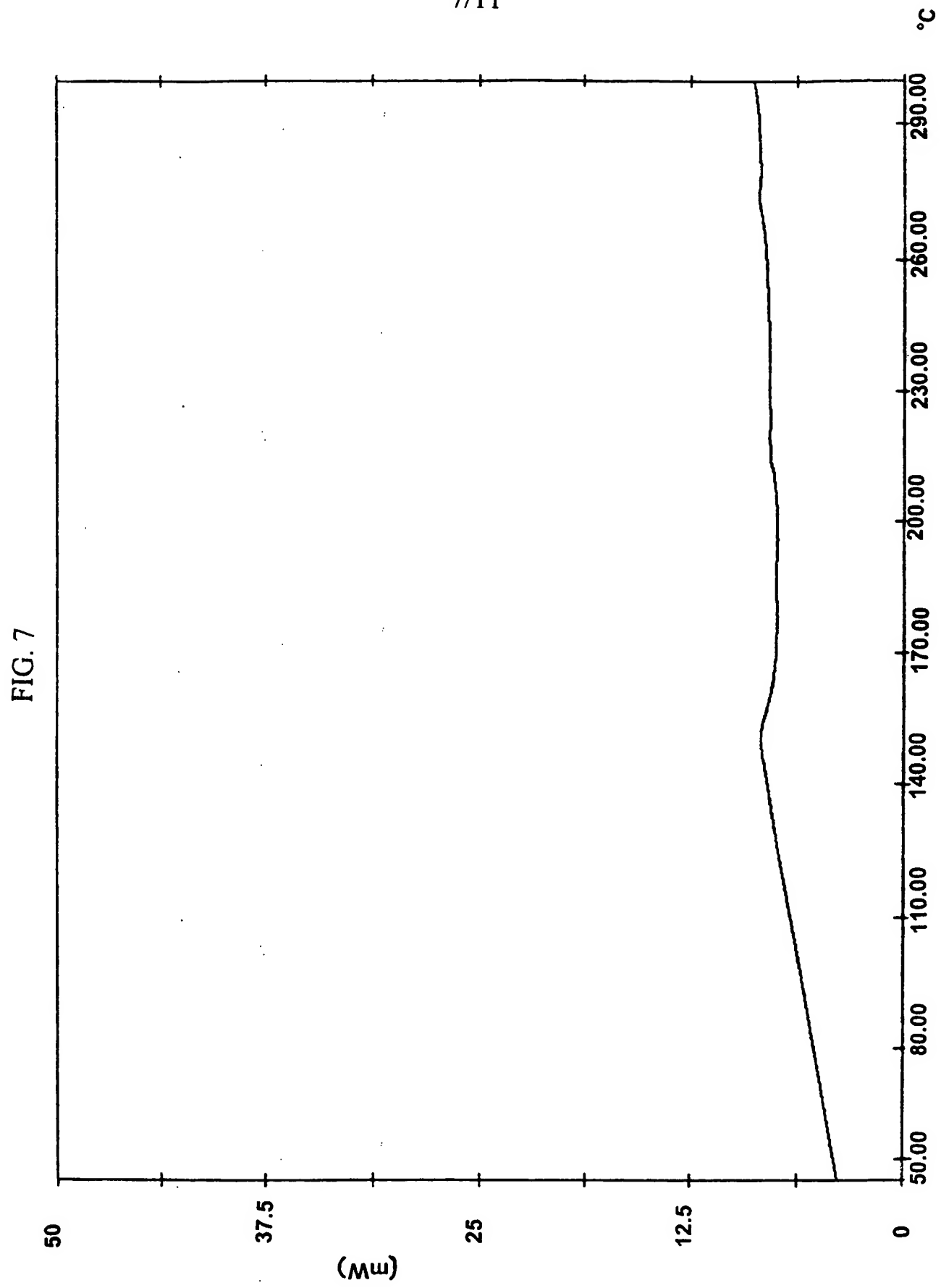
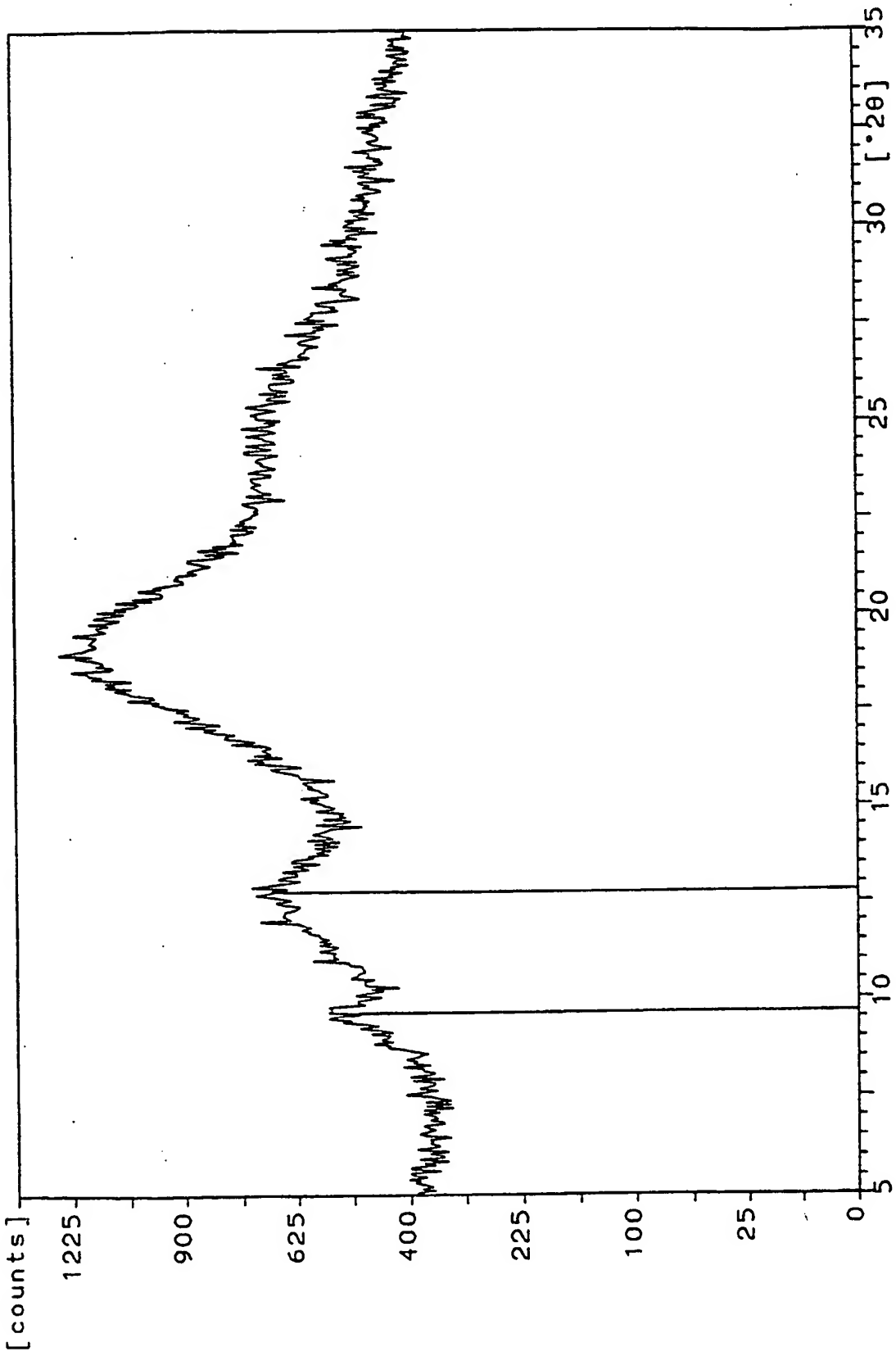

°C
290.00
260.00
230.00
200.00
170.00
140.00
110.00
80.00
50.00
50
37.5
25
12.5
0
(mW)

FIG. 7

FIG. 8



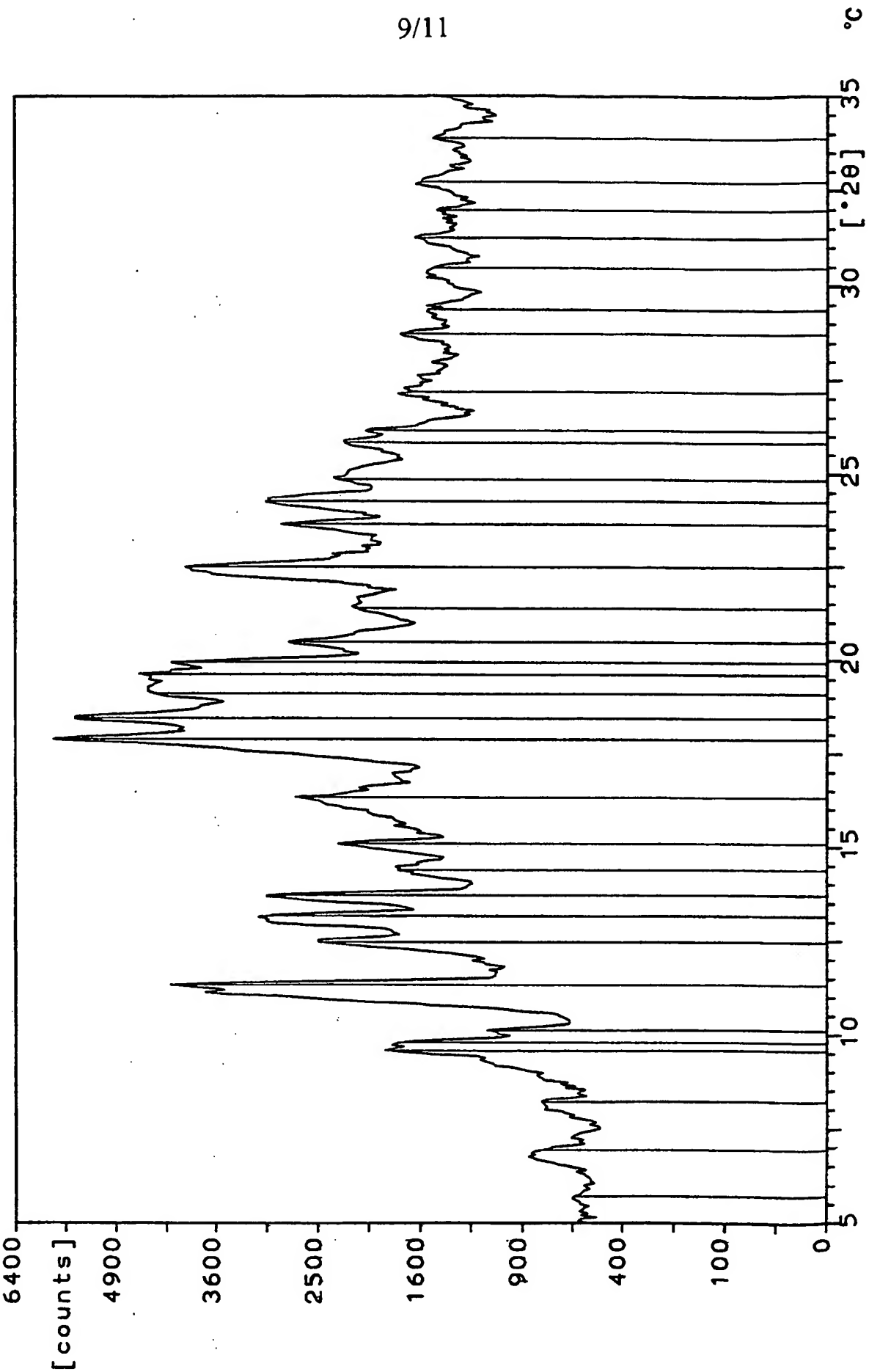

6400
4900
3600
2500
1600
900
400
100
0
[counts]
5
10
15
20
25
30
35
[°2θ]
°C

FIG. 9

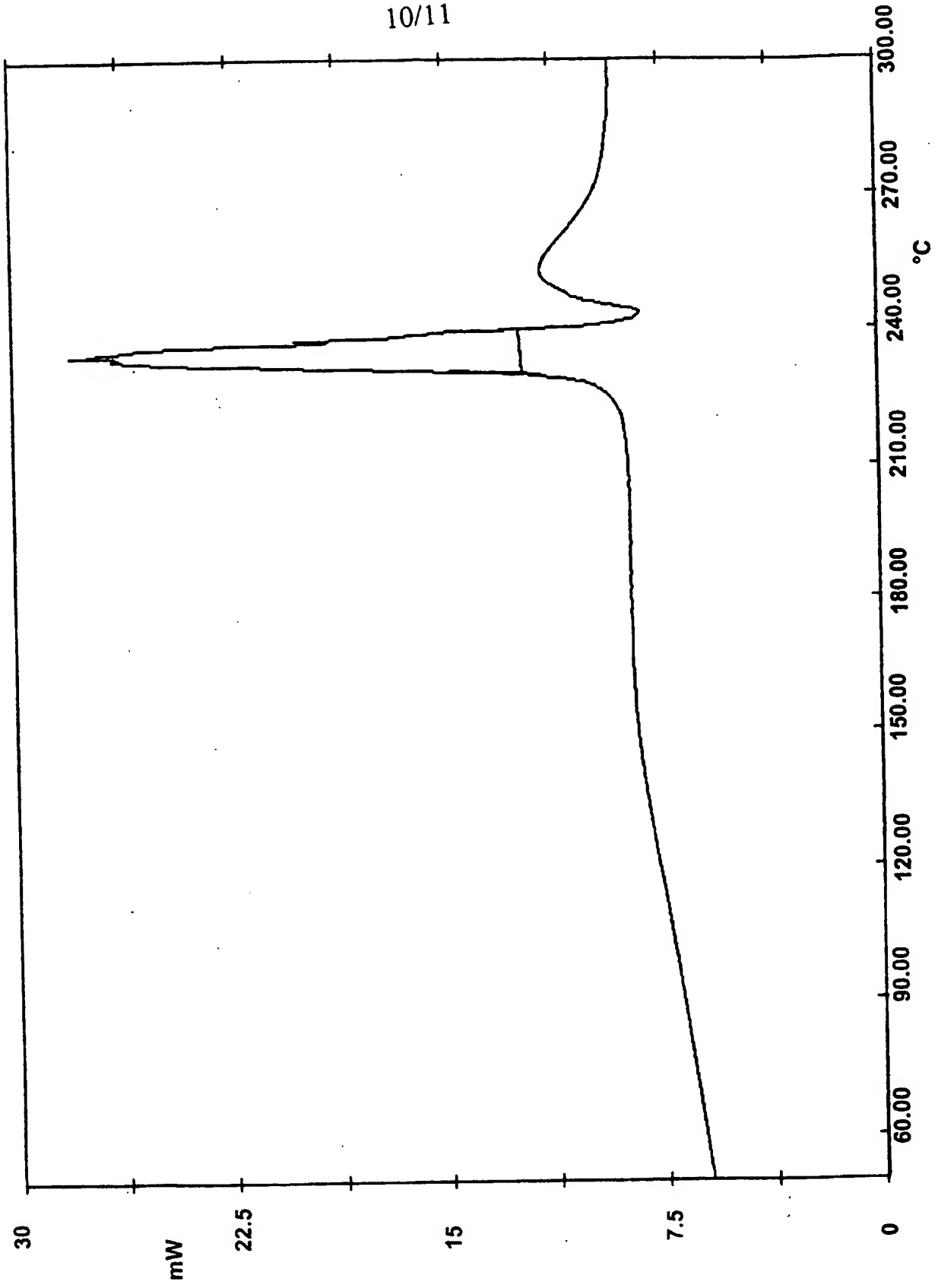

300.00
270.00
240.00
210.00
180.00
150.00
120.00
90.00
60.00
°C
30
22.5
15
7.5
0
mW

FIG. 10

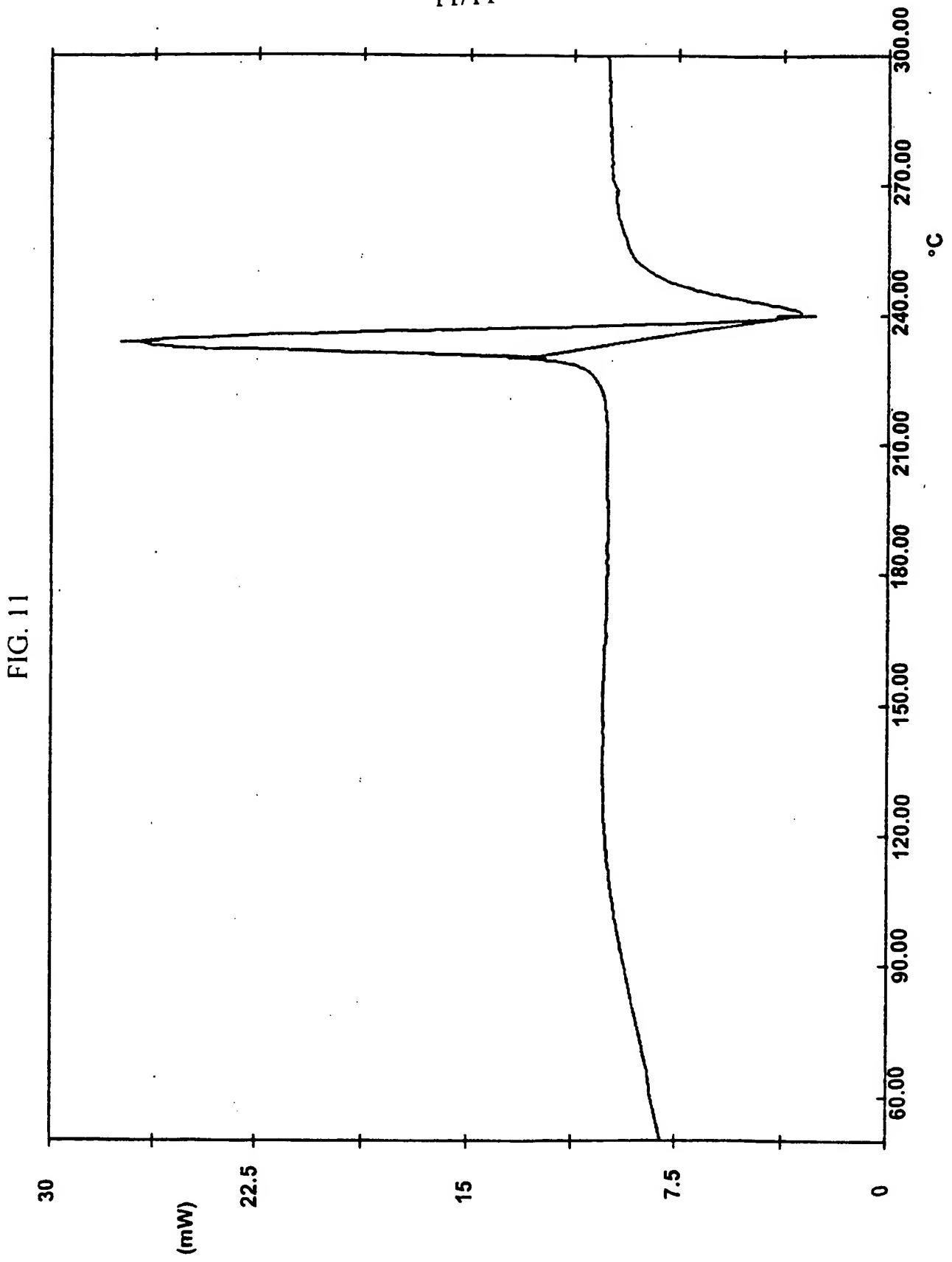

300.00
270.00
240.00
210.00
180.00
150.00
120.00
90.00
60.00
°C
30
22.5
15
7.5
0
(mW)

FIG. 11

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 00/06121

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/12 C08B37/00 A61K31/445 A61K31/4525 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C08B A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 007 196 A (J.A. CHRISTENSEN) 8 February 1977 (1977-02-08) column 1 -column 10	1,7,8, 11,26,27
P,A	WO 00 08016 A (SMITH-KLINE-BEECHAM) 17 February 2000 (2000-02-17) claims	1,7,11, 26,27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 October 2000	16/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/06121

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 4007196 A	08-02-1977	GB	1422263 A	21-01-1976
		BE	893095 A	30-08-1982
		AT	333759 B	10-12-1976
		AT	69674 A	15-04-1976
		BE	810310 A	16-05-1974
		CA	1038390 A	12-09-1978
		CH	592059 A	14-10-1977
		DE	2404113 A	08-08-1974
		DK	149843 B	13-10-1986
		ES	422734 A	01-04-1976
		FI	57932 B	31-07-1980
		FR	2215233 A	23-08-1974
		HK	13081 A	10-04-1981
		IE	38801 B	07-06-1978
		IT	1054157 B	10-11-1981
		JP	1268487 C	10-06-1985
		JP	49101385 A	25-09-1974
		JP	59046216 B	10-11-1984
		JP	1272362 C	11-07-1985
		JP	58174363 A	13-10-1983
		JP	59048826 B	29-11-1984
		LU	88398 A	04-05-1994
		LU	69264 A	10-04-1974
		NL	7401189 A,B,	01-08-1974
		NO	144568 B	15-06-1981
		PH	10383 A	02-03-1977
		SE	401827 B	29-05-1978
		US	3912743 A	14-10-1975
WO 0008016 A	17-02-2000	AU	5294899 A	28-02-2000
		AU	5294799 A	28-02-2000

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 02/00134

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 48499 A (SMITHKLINE BEECHAM) 30 September 1999 (1999-09-30) the whole document	1-10
A	WO 00 78288 A (SMITHKLINE BEECHAM) 28 December 2000 (2000-12-28) the whole document	1-10
P,A	WO 01 58449 A (SMITHKLINE BEECHAM) 16 August 2001 (2001-08-16) the whole document	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 July 2002	29/07/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Ventura Amat, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK 02/00134

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9948499 A	30-09-1999	AU 3045199 A	18-10-1999
		BG 104865 A	31-05-2001
		BR 9908991 A	12-12-2000
		CA 2324612 A1	30-09-1999
		CN 1294512 T	09-05-2001
		EP 1063993 A1	03-01-2001
		WO 9948499 A1	30-09-1999
		JP 2002507569 T	12-03-2002
		NO 20004740 A	03-10-2000
		PL 343095 A1	30-07-2001
		SK 14102000 A3	12-03-2001
		TR 200002750 T2	21-12-2000
WO 0078288 A	28-12-2000	AU 5550700 A	09-01-2001
		WO 0078288 A2	28-12-2000
WO 0158449 A	16-08-2001	AU 3207901 A	20-08-2001
		WO 0158449 A1	16-08-2001